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NAPHTHYRIDINONE ANTIMALARIAL PROPHYLACTICS

FINAL TECHNICAL REPORT

for

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By

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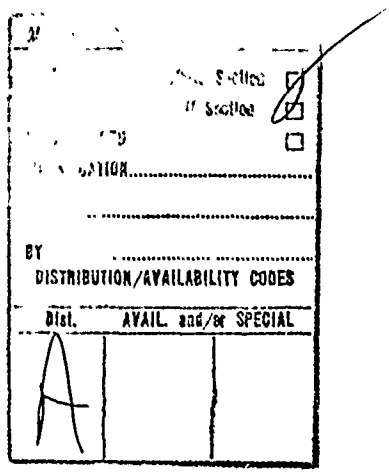

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1. SUMMARY

4-Amino-1,5-naphthyridines have been envisioned as structural contours of both 4-amino and 8-aminoquinoline antimalarial agents. These derivatives have, however, only been effective against the asexual erythrocytic stages of the parasite. None of the reported variations show the prophylactic behavior characteristic of 8-aminoquinoline drugs. Recently we reported that oxidation of the 1,5-naphthyridine nucleus to the 1,5-naphthyridin-2-one resulted in drugs responsive to the Schmidt prophylactic antimalarial screen.

The work detailed herein was an attempt to amplify on our earlier finding through (a) further alterations of the naphthyridin-2-one nucleus and (b) attachment of diamino sidechains noted to be significant to the prophylactic agents pamaquine, pentaquine, primaquine, and quinocide. The latter two types of sidechains received particular emphasis.

In general, target drugs were obtained in 50-90% yield by a high temperature reaction of a diaminoalkane with a 4-chloro-1,5-naphthyridin-2-one. Although 1-(H) and 1-Me naphthyridinone syntheses have been reported we experienced considerable difficulty in reproducing the reported yields and purity. Modification of the reported experimental and isolation procedure proved to be the best of several alternative synthesis of 4-chloro-1,5-naphthyridin-2-ones. A new synthetic entry into 4-chloro-1-methyl-1,5-naphthyridin-2-one synthons evolved during this contractual period. The new technique is superior to reported procedures in terms of its generality, yield, and freedom from contamination by isomeric naphthyridines. In addition, integrity of acid sensitive functionality was maintained during the synthesis of the 1-methyl 1,5-naphthyridin-2-ones. In essence the new preparative method involves N-methylation of 4-chloro-1,5-naphthyridine followed by oxidation of the naphthyridinum salt.

Seven target drugs substituted at C-4 of the 1,5-naphthyridin-2-ones by pamaquine and pentaquine sidechains were prepared. Five of these drugs was obtained by reaction of the commercially available diaminoalkane with the appropriate naphthyridinone synthon. Acid catalyzed hydrolysis of those drugs substituted by 6-butoxy functionality yielded the corresponding 6-hydroxy derivatives.

Because 1,4-pentanediamines, masked on either amino termini were unknown at the inception of this program introduction of the primaquine and quinocide sidechain into the naphthyridinone nuclei required a different synthetic approach. Attachment of the primaquine sidechain could be realized by reaction of 4-amino-1-pentanol with 4-chloro-1,5-naphthyridin-2-ones and in several steps transform the hydroxyl terminated sidechain into the primary amino function. The overall yield from this sequence of reaction is extremely poor.

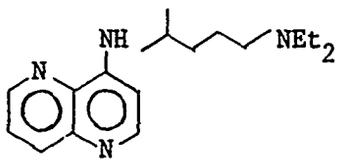
Starting with 4-amino-1-pentanol a series of synthetic steps was devised which permitted us to realize synthesis of the previously unknown isomeric "masked" 1,4-pentanediamines. These isomeric aminoalkanes were readily attached to the naphthyridinone ring via the nucleophilic

displacement of C-4 chlorine. The target drugs substituted by sidechains having primaquine and quinocide configuration were isolated in good yield as crystalline solids. Cleavage of the acetamido masking function from these drugs was achieved by base catalyzed hydrolysis. Acidic hydrolytic conditions destroyed the entire sidechain.

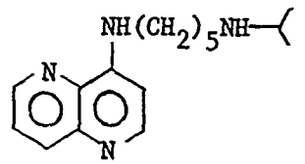
A total of 18 target drugs substituted in the 1,5-naphthyridin-2-one C-4 position by diaminoalkane functions was synthesized during this contract. No biological data is yet available.

2. INTRODUCTION

The potential biosteric equivalency of the quinoline and naphthyridine nuclei has attracted synthetic and biological attention for a number of years.[1-4] Most recent synthetic efforts by McCaustland and Cheng[3] were an attempt to emulate the biological response of both 4-amino- and 8-aminoquinoline antimalarial drugs. These authors, as with earlier investigators, succeeded in the synthesis of naphthyridine variants of the type A,



A

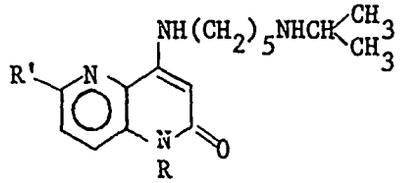


B

wherein the ring substitution patterns were of the variety found desirable for both 4-amino- and 8-aminoquinoline antimalarial agents. In those cases where the drugs were active the efficacy was against the asexual erythrocytic stages of the parasite.[5] This is characteristic of the 4-aminoquinoline drugs. In spite of the structural identity of certain type A compounds to the 8-aminoquinoline prophylactic agent pamaquine no gametocytocidal efficacy was noted for the naphthyridine analogs. In an earlier synthetic effort in our laboratories[4] we found that variation in the basic sidechain such that type B naphthyridines were structural contours of the gametocytocidal drug pentaquine similarly failed to produce a prophylactic response.

It is apparent from the above cited studies that the nitrogen at the 1-ring position dominates the manner in which the malaria parasite responses to a drug regime of 4-amino-1,5-naphthyridine derivatives. We rationalized that in order to solicit a biological response akin to the 8-aminoquinoline antimalarials a change in the electronic character of N-1 needed to be effected.

The merits of this type of reasoning were validated by the biological response of the three drugs prepared in our laboratories in an earlier contract.[4]



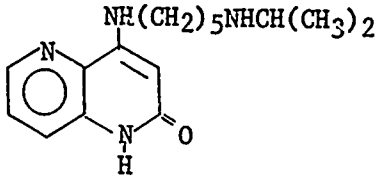
WR 206287 - R=R'=H
WR 222119 - R=CH_3, R'=H
WR 222121 - R=CH_3, R'=CF_3CH_2O

All three of the naphthyridinone derivatives proved to be active in the Schmidt prophylactic screen.

The work detailed in this report was aimed at a further exploitation of the prophylactic behavior of 4-amino-1,5-naphthyridin-2-ones. Particularly emphasized was the attachment of primaquine and quinocide type diamino sidechains to the naphthyridin-2-one C-4 position.

3. TARGET COMPOUNDS SUBMITTED

Pentaquine Chain



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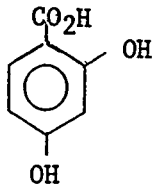

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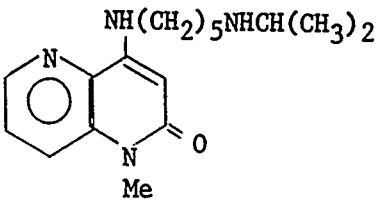

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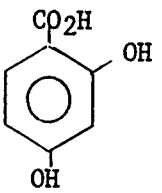

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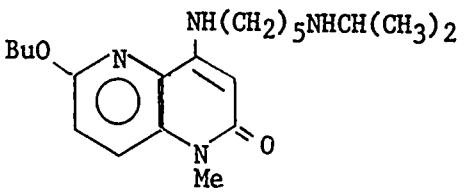

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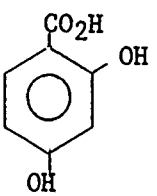

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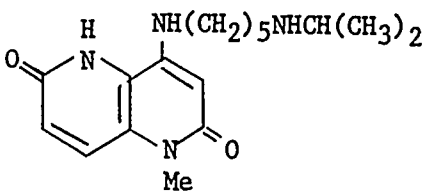

• 2 HCl

NT-31
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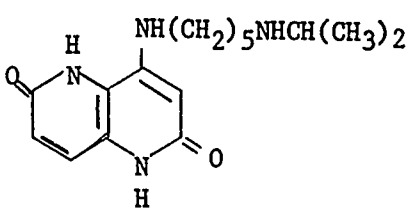
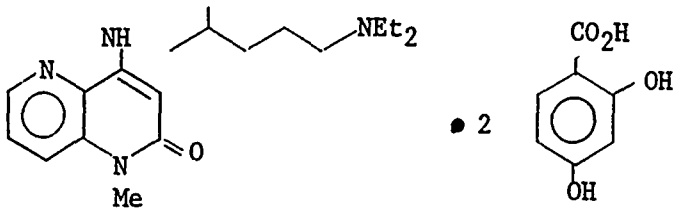
(BH01032)



• HCl

NT-39
(662-48)

Pamaquine Chain



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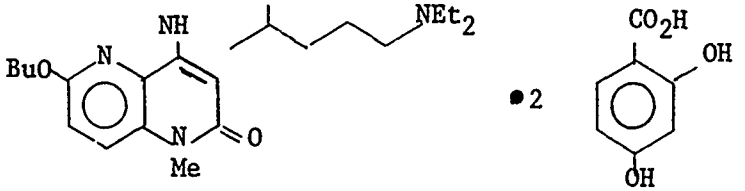
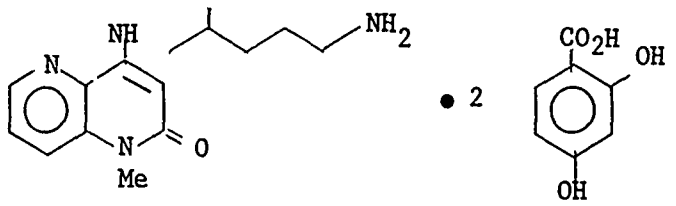
(BG89362)



NT-40
(662-67)

Primaquine Chain



NT-28
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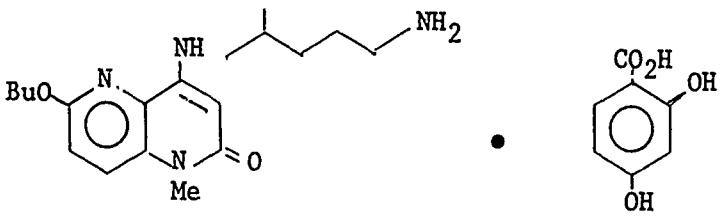
(BG89371)



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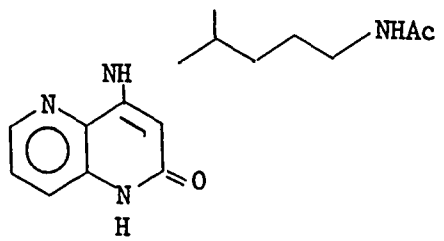

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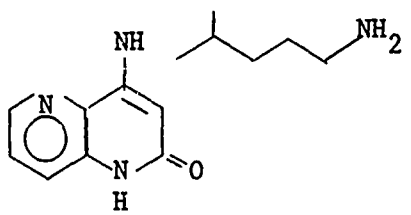
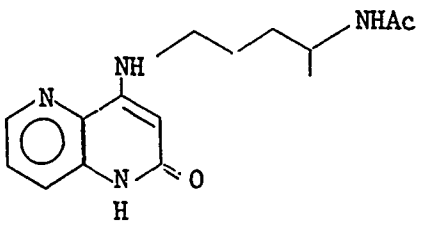
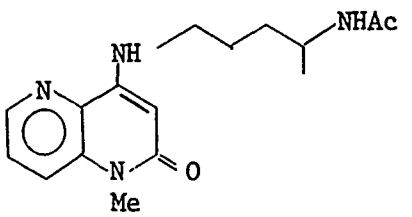


NT-29
(662-70)

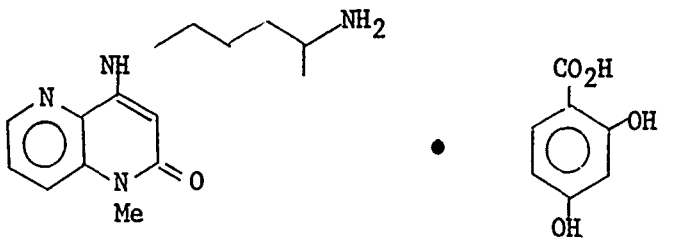
Quinocide Chain



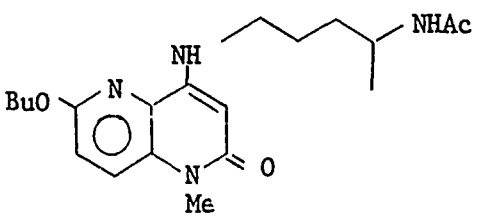
NT-36
(662-66)
(BH27483)



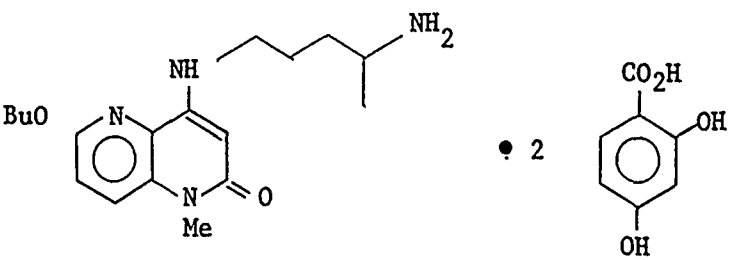
NT-34
(662-62)
(BH12768)



NT-37
(662-68)
(BH27492)



NT-35
(662-64)



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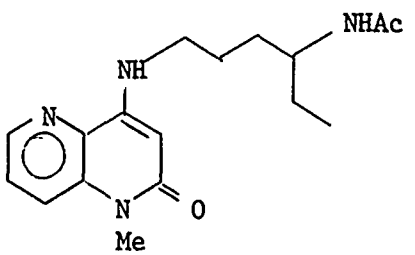

NT-32
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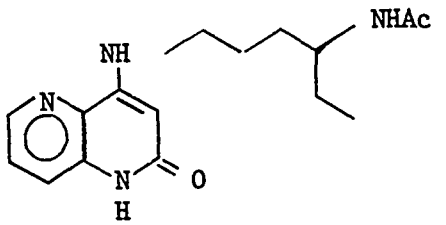
Quinocide Chain (cont'd.)



NT-33
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(BH12768)

4. DISCUSSION

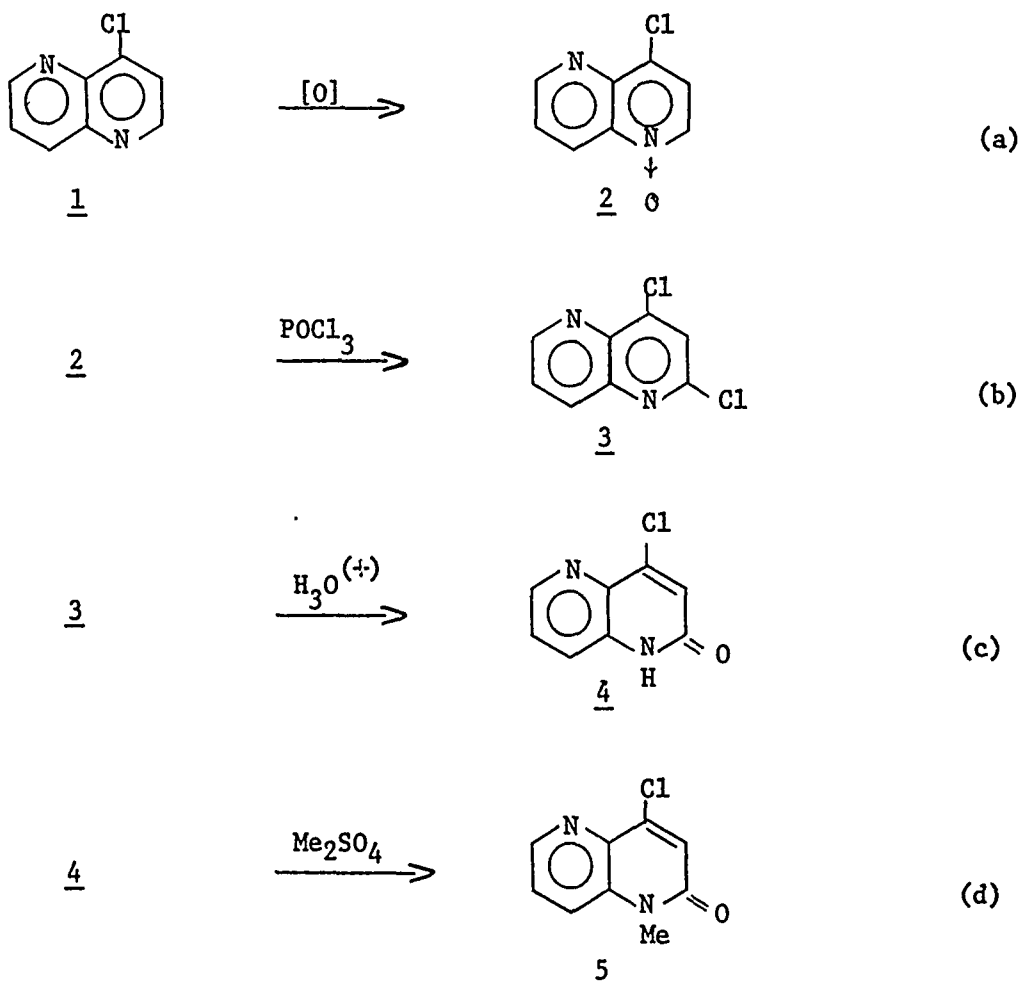
The synthetic program described herein--aimed at the preparation of 4-amino-1,5-naphthyridin-2-ones--was basically a two phase program. The initial phase consisted of devising reliable synthetic entries to precursor 1,5-naphthyridin-2-ones. Although several synthons of this type have been reported(3,4,6) the preparative methods proved to be irreproducible and/or accompanied by undesirable and difficult to remove isomeric naphthyridines. In the second phase, namely the insertion of diamino functions, at the ring position C-4, also required development of new synthetic techniques.

The following section details, sequentially, the preparative methods to (a) naphthyridinone precursors, (b) target drugs and (c) previously unrecorded "masked" 1,4-pentanediamines.

4.1 4-Chloro-1,5-naphthyridin-2-ones

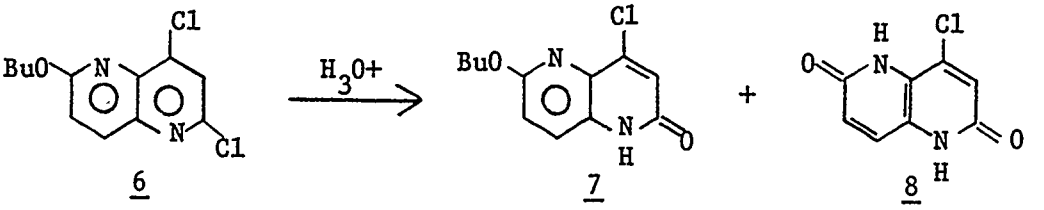
The synthons 4 and 5 are reported to be accessible via the sequence of reactions shown in Scheme 1.

Scheme 1



Although this sequence is operative as shown, the yields and purity for steps (c) and (d) were difficult to consistently reproduce. Because of the significance of these two naphthyridinones to our synthetic efforts, attempts were made to improve the syntheses leading to 4 and 5.

Through the adjustment of experimental conditions and product isolation, the conversion of 3 to 4 was improved to 85%. This process improvement is detailed in the Experimental Section. The strong acid catalyzed hydrolysis of C-2 chlorine when attempted with the naphthyridine 6 did not yield significant quantities of 7. The major product was a yellow high melting solid. Spectral data (Figure 1) and elemental analysis indicated that the hydrolytic condition stripped the molecule of C_2 chlorine and also the 6-butoxy function. Structural assignment of 8



6 7 8

to the indicated tautomer was supported by its electronic absorption spectrum (maxima at 355, 370, and 390 nm). These values are in good agreement with Rapport's[7] reported absorption maxima for the related 1,5-dimethyl-1,5-naphthyridin-2,6-dione.

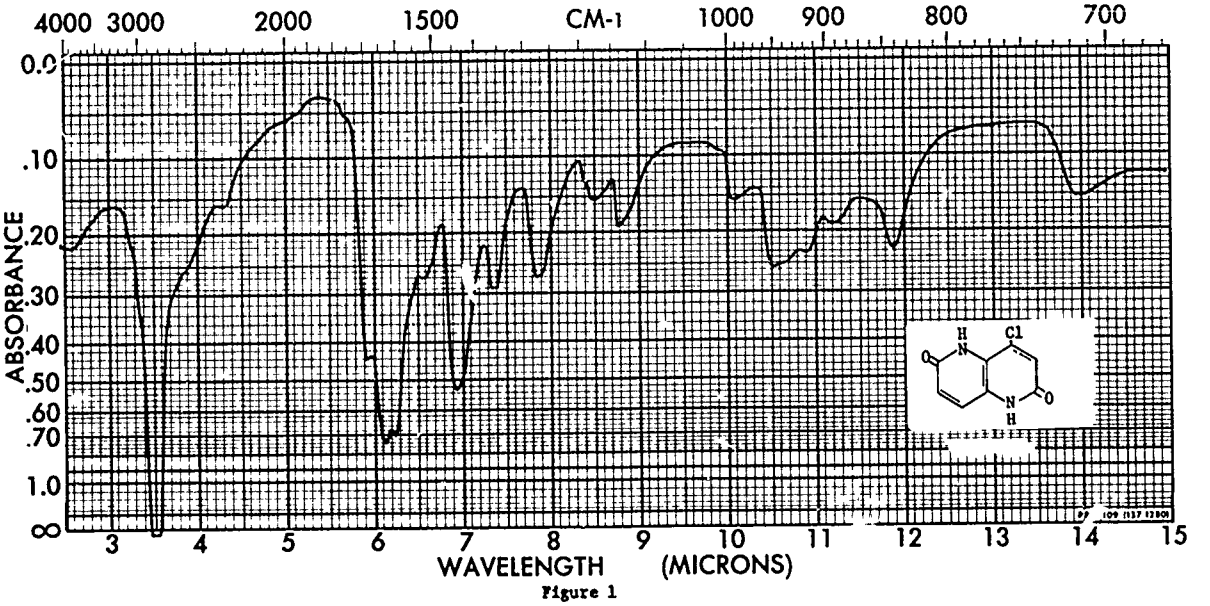
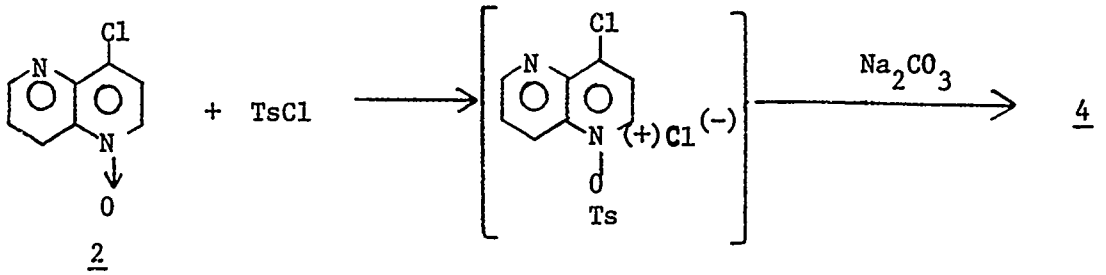


Figure 1

In order to avoid cleavage of the 6-butoxy function as well as a desire to circumvent synthetic step (b) we evaluated the feasibility of directly converting 2 → 4 as shown.

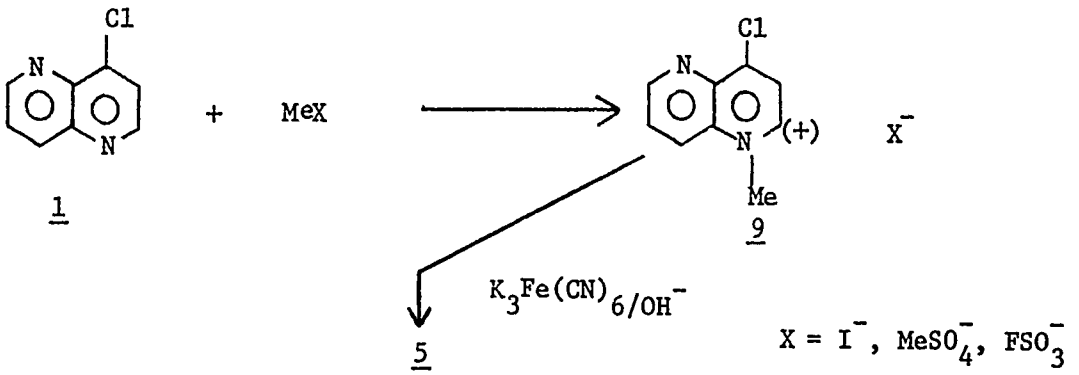


2

The conversion of quinoline-N-oxide to the corresponding carbostyrils via the above technique is reported(8) to proceed in better than 50% yield. Application of this oxidative procedure to the 1,5-naphthyridine system effect the conversion of 2 → 4 in about 20%. Further studies with this synthetic method were abandoned in favor of the process indicated by step (b).

During the course of this contractual period a new synthetically superior technique for preparation of N-alkyl naphthyridin-2-ones was developed. In this new procedure, as shown in Scheme 3, the transformation of 1 to 5 was realized in good yield and with the elimination of two synthetic steps necessitated by the sequence shown in Scheme 1. Unlike the reported procedures this new technique yielded 5 uncontaminated by the O-methylated tautomers namely 4-chloro-2-methoxy-1,5-naphthyridine

Scheme 2



1 9 5

Alkylation of 1 was effected with a variety of reagents. Initially the naphthyridinium salt 9 was prepared with methyl iodide. However, the iodide gegenion caused 9 to have a very low water solubility and the subsequent aqueous ferricyanide oxidation required an unacceptably large volume of water. The use of dimethyl sulfate or fluoromethyl sulfonate ["magic methyl" (Aldrich)] gave 9 as a readily water soluble salt. Fluoromethylsulfonate gave 9 in virtually quantitative yield in 0.5 hr reaction time. The infrared spectrum 9, as the methylsulfonate salt, is shown in Figure 2.

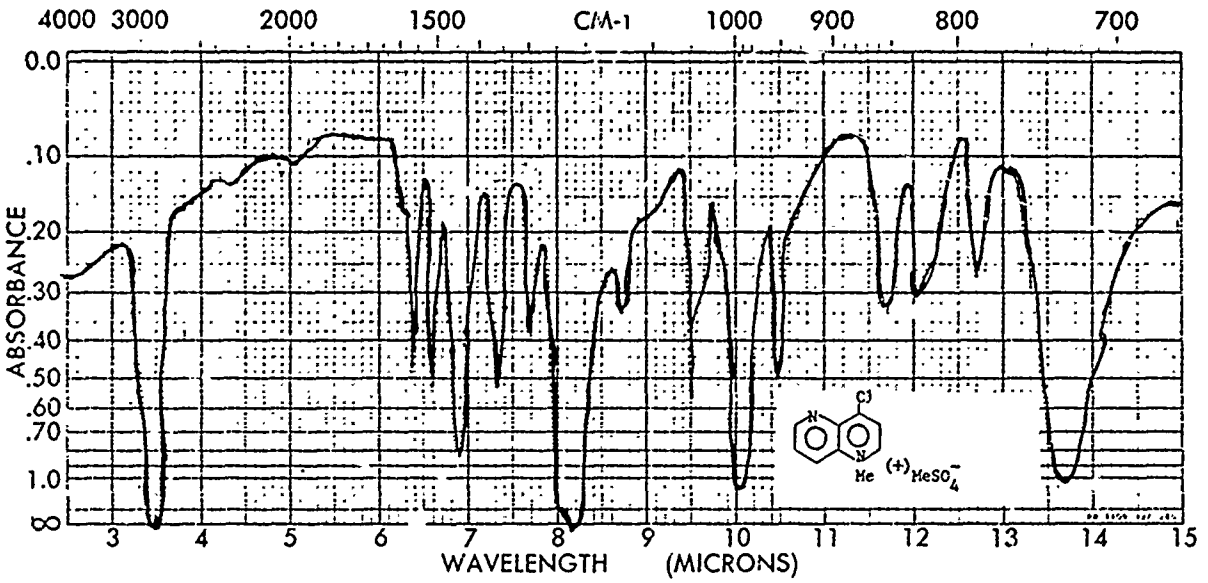
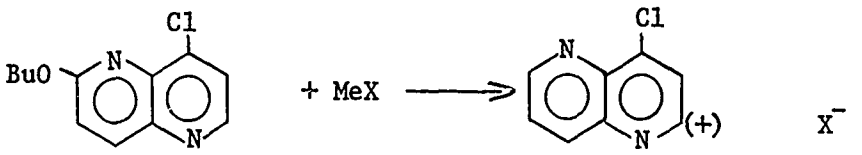


Figure 2

Alkylation of the naphthyridine 10 was also achieved with either dimethyl sulfate or "magic methyl" to give 11 in virtually quantitative yield.



10 11

The proton spectrum (Figure 3) of 11 shows the ring protons in the anticipated AB patterns (two sets) and clearly establishes that the acid sensitive 6-butoxy function is intact.

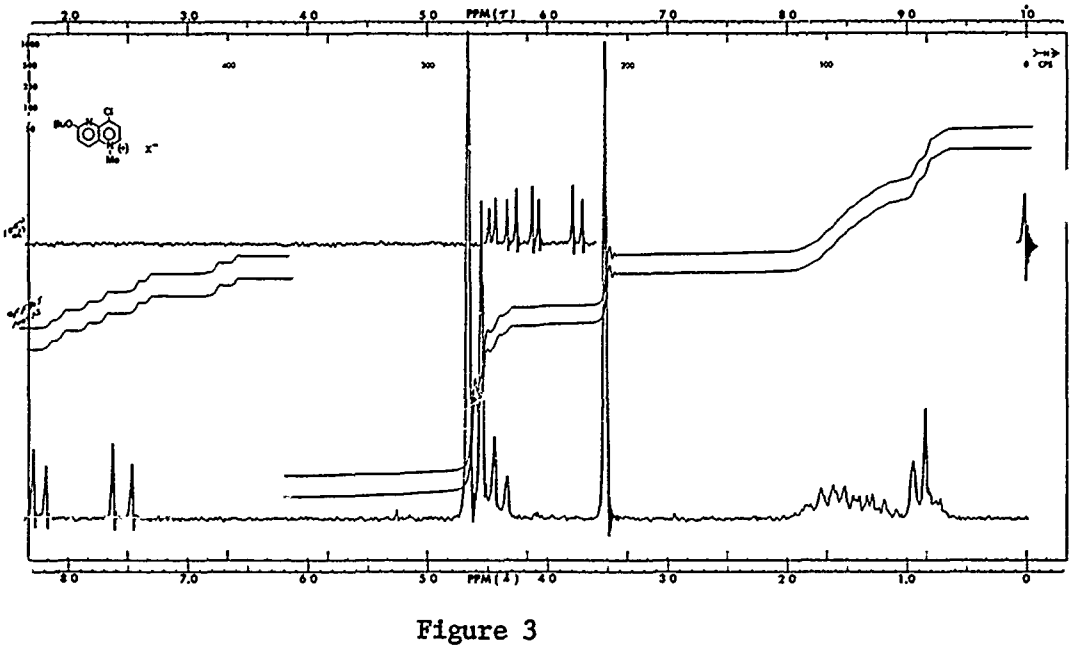
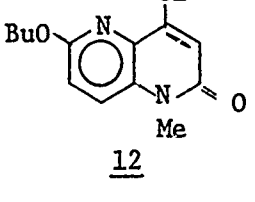


Figure 3

The oxidation of 9 and 11 was realized without synthetic entanglement essentially as Rapoport[7] described for the oxidation of the parent 1,5-naphthyridinum salt. The infrared spectrum of 12 is given in Figure 4.



12

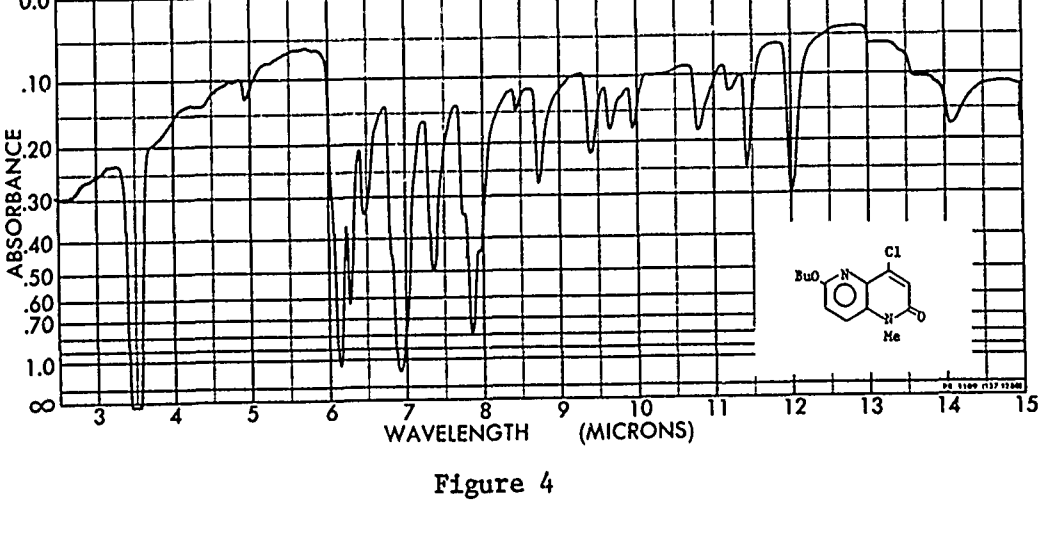
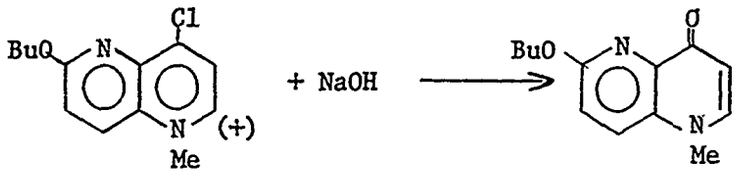


Figure 4

The only problem encountered with the oxidation of naphthyridinum salts was when the reaction temperature and base concentration was not suitably monitored. Apparently as the experimental conditions become more rigorous the nucleophilic displacement of C-4 chlorine becomes a significant competitor to the desired oxidation of C-2.



11 13

The four ring protons appearing in Figure 5 as two AB patterns (δ 6.2-7.9) are in accord with the structural assignment of 13.

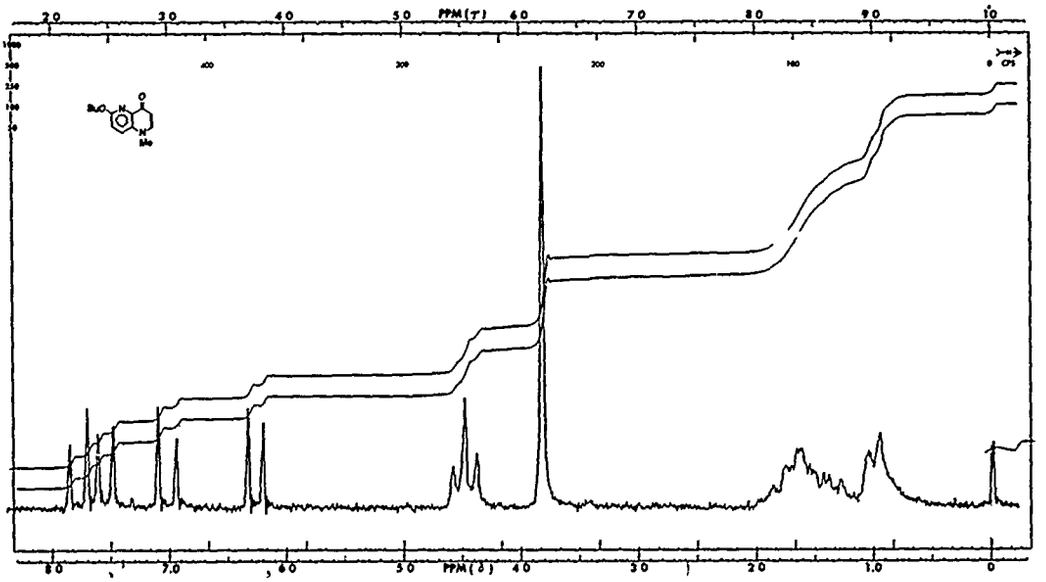
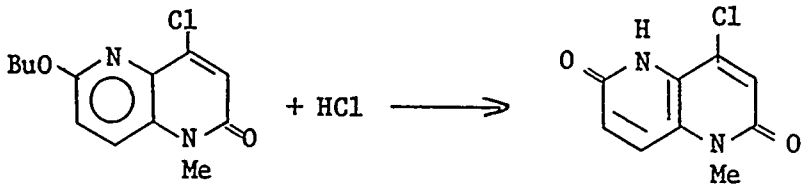


Figure 5

The naphthyridin-2-one 12, was converted in quantitive yield with concentrated hydrochloric acid to the new synthon, 4-chloro-1,5-naphthyridin-2,6-dione 14. Figure 6 represents the infrared spectrum of 14.



12 14

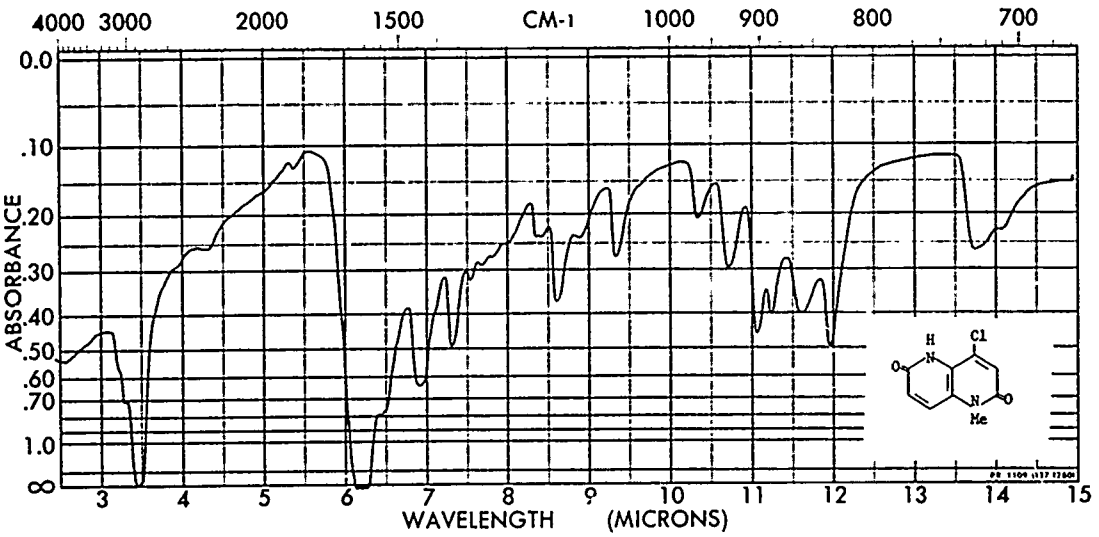
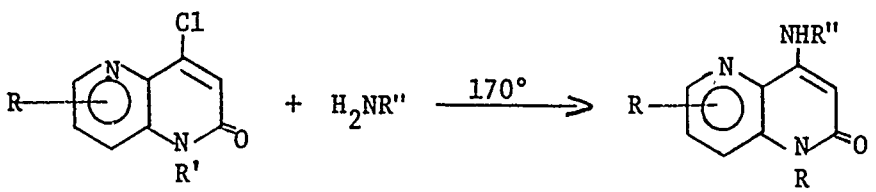


Figure 6

4.2 Target 4-Amino-1,5-Naphthyridin-2-ones

The target drug compounds prepared were available, generally in moderate to good yields by simply heating the appropriate naphthyridin-2-one synthon with several molar equivalents of an amine. Initially it was felt



that attachment of the amino function to the C-4 position of the heterocycle required copper-bronze in catalytic quantities. Later syntheses were found to be equally effective without the copper-bronze.

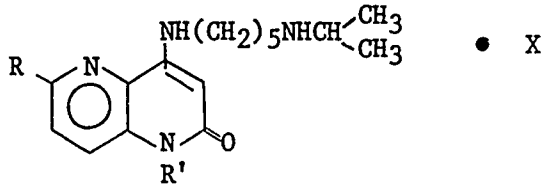
For reasons which we will present below, introduction of the primaquine and quinocide type sidechain required certain modification of the general sidechain attachment procedure.

In the following section the drugs synthesized will be discussed according to the type of sidechain introduced. Except where indicated, the target drugs were converted to the β-resorcyclic acid salts for submission to the WRAIR antimalarial screening program.

4.2.1 PENTAQUINE SIDECHAIN
4-(5-Isopropylaminopentylamino)-1,5-Naphthyridin-2-ones

Drugs of this category, substituted at the naphthyridin-2-one C-4 position with the diamino function present in the prophylactic drug pentaquine were all isolated as crystalline solids. The specific drug structures are shown in Table 1.

TABLE 1



NT	NB#	R	R'	X*
NT-7R	662-10	H	H	A
NT-25	--	H	Me	A
NT-30	662-31	BuO	Me	A
NT-31	662-35	HO	Me	B
NT-39	662-48	HO	H	B

*A = β Resorcylic acid; B = HCl

Typical of this class of target drugs is the proton spectrum of the free base of NT-30 (Figure 7).

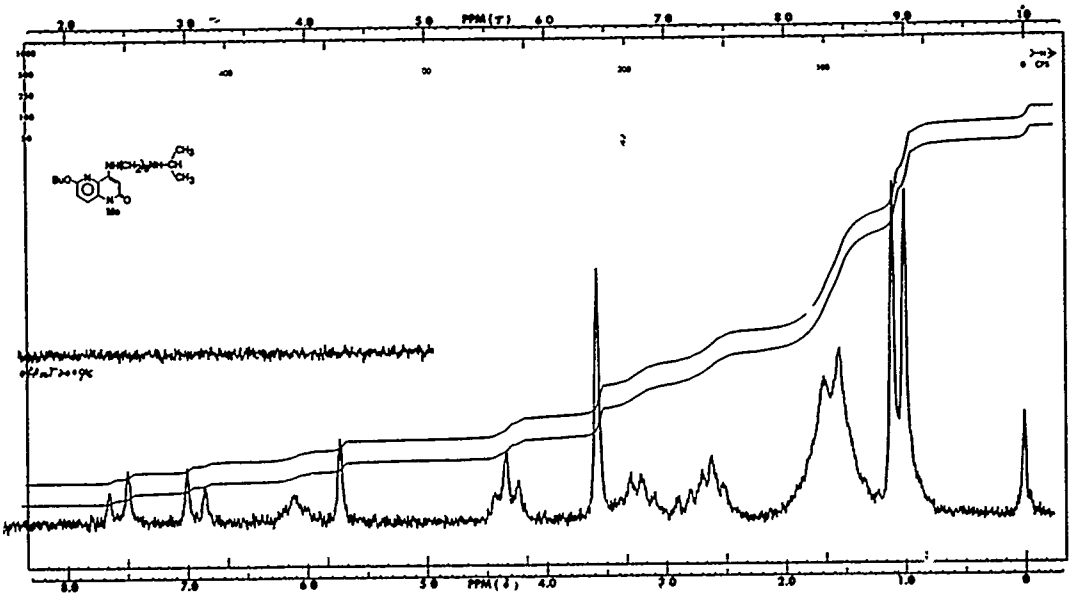
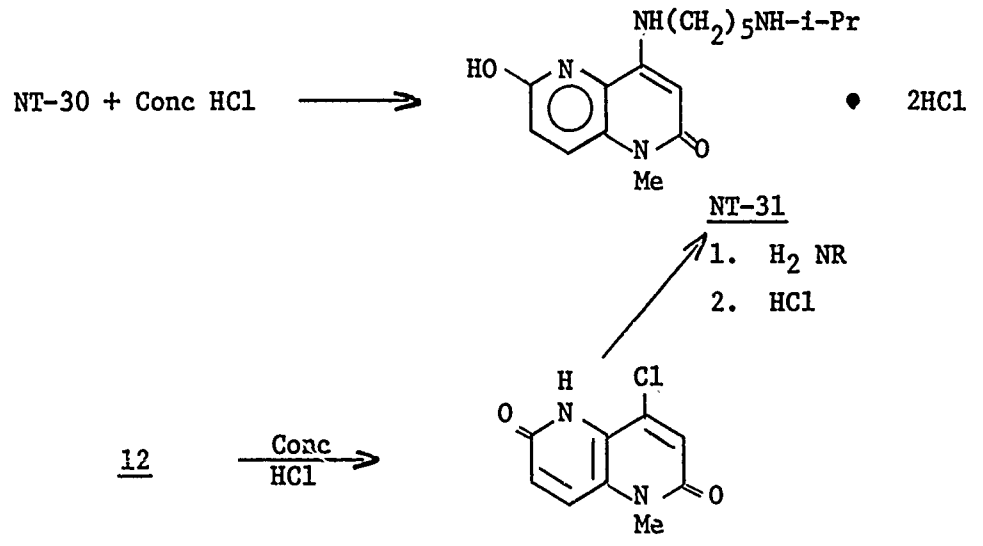


Figure 7

The distinguishing features being doublet at δ 1.08 (6H, CH-($C\underline{H}_3$)$_2$) singlet at δ 3.58 (3H, NCH_3) and the single at δ 5.71 (1H ring proton at C_4).

Heating NT-30 with concentrated HCl effected a facile dealkylation of the 6-butoxy function to give target compound NT-31.



14

The proton spectrum of NT-31 (Figure 8) clearly indicated that dealkylation of the 6-butoxy function occurred without loss of the diamino sidechain. Conformation of the indicated structural change was apparent from the dealkylation of the synthon 12 to give the naphthyridin-2,6-dione 14 followed by reaction of 14 with isopropylaminopentylamine. The product from either of the indicated routes is identical.

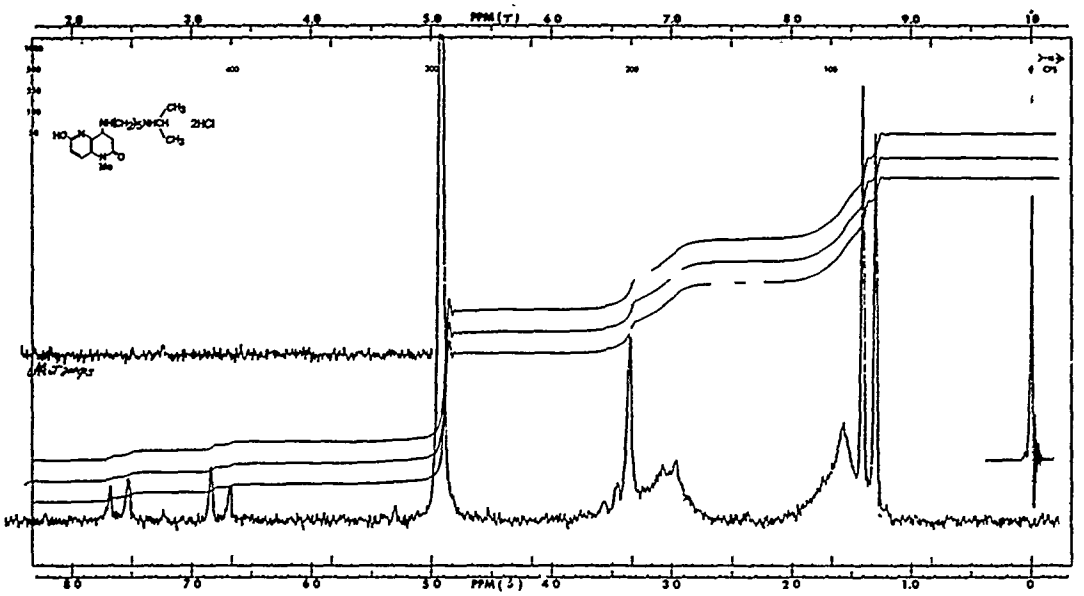


Figure 8

It is worth noting that the dealkylation of 12 yields 14 in which spectral data indicates it to be a 1,5-naphthyridin-2,6-dione derivative. In contrast to this, dealkylation of NT-30 or amination of 14 yielded not a naphthyridin-2,6-dione derivative but the tautomer having the indicated structure. The structural assignment of NT-31 can be rationalized from the electronic spectra. The argument is as follows:

Rapoport and Batcho[7] have shown that the absorption max of 1-methyl-1,5-naphthyridin-2-one is shift from 330-340 nm to 380-410 nm upon oxidation to the corresponding naphthyridin-2,6-dione. Figure 9 shows that the absorption maximum of the naphthyridin-2-one 14 experiences on analogous red shift from 340-380 nm to >410 nm as a consequence of dealkylation. Based on this, one can feel confident that 14 is in the tautomeric form indicated.

However, as shown in Figure 10, dealkylation of NT-30 does not produce the magnitude and directional spectral shift characteristic of naphthyridin-2,6-diones. Therefore, it would be inappropriate to depict NT-31 as a naphthyridin-2,6-dione derivative.

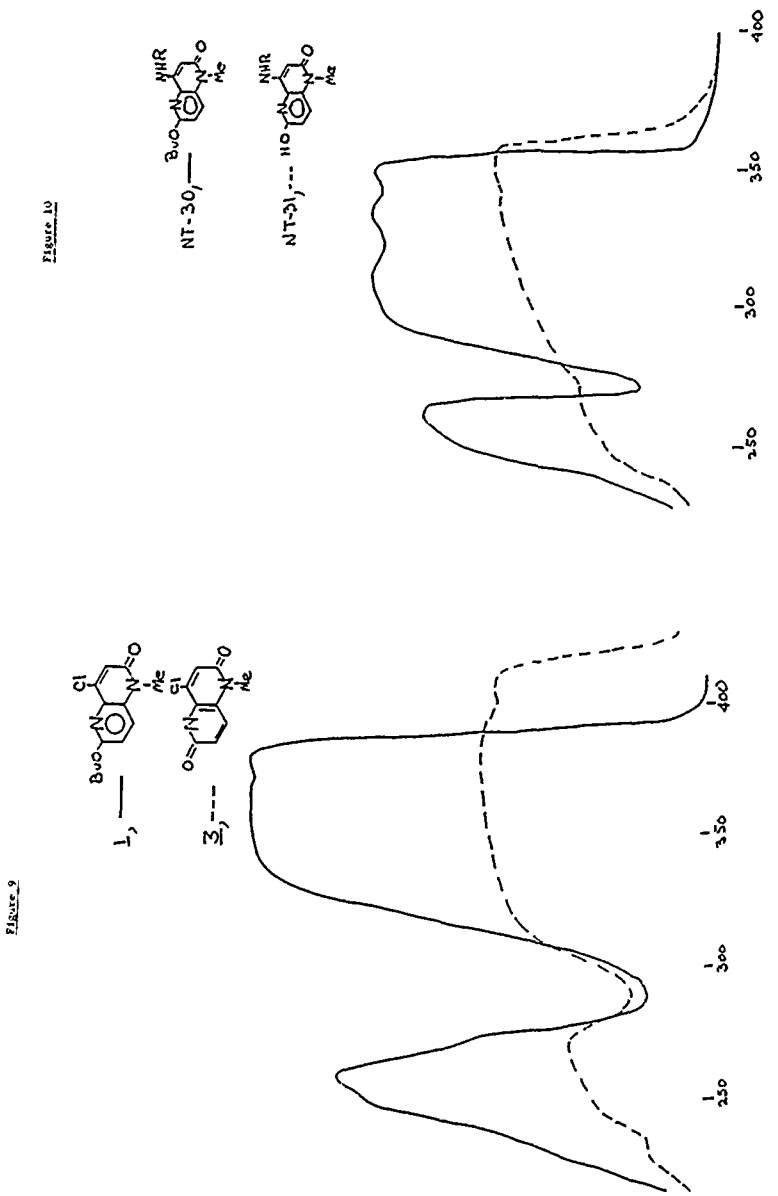


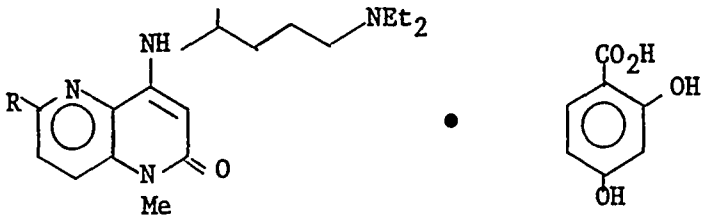
Figure 9

Figure 10

4.2.2 PAMAQUINE SIDECHAINS

4-(4- Diethylamino-1-methylbutylamino)1,5-Naphthyridin-2-ones

The commercial availability of the requisite diaminoalkane makes the attachment of the pamaquine sidechain to the naphthyridin-2-one nuclei a standard displacement of C-4 chlorine by the diaminoalkane. Derivatives of this class of target drugs were isolated as viscous liquids. Compounds NT-27 and NT-40 were prepared and submitted as β-resorcylic acid salts.



NT-27, R = H

NT-40, R = OBu

The infrared spectrum of NT-27 and NT-40 as their free bases, are given in Figures 11 and 12.

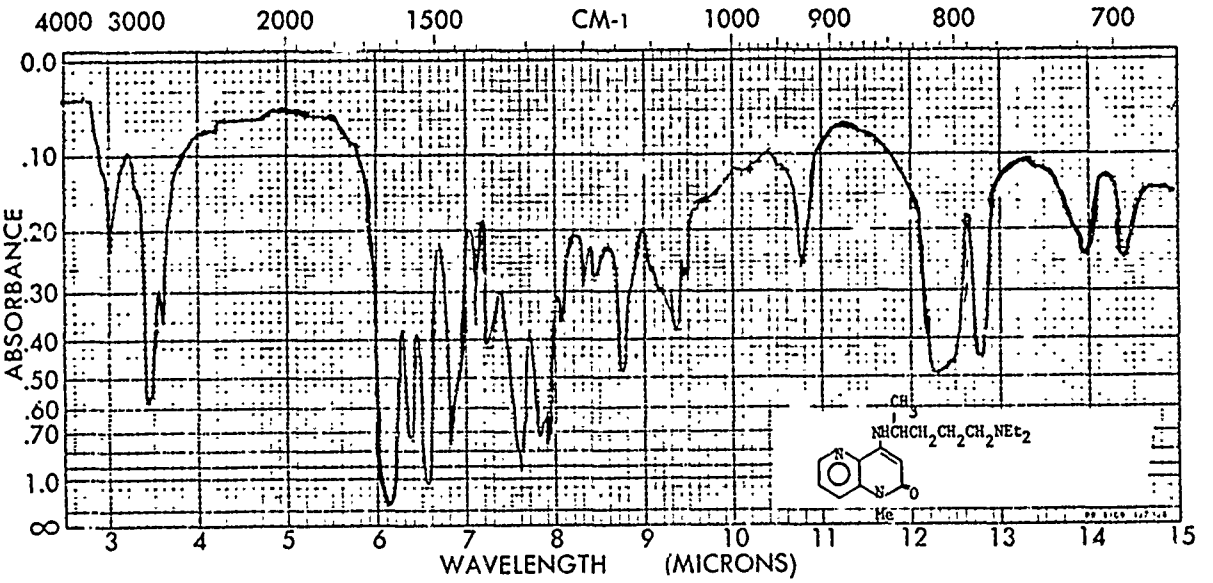


Figure 11

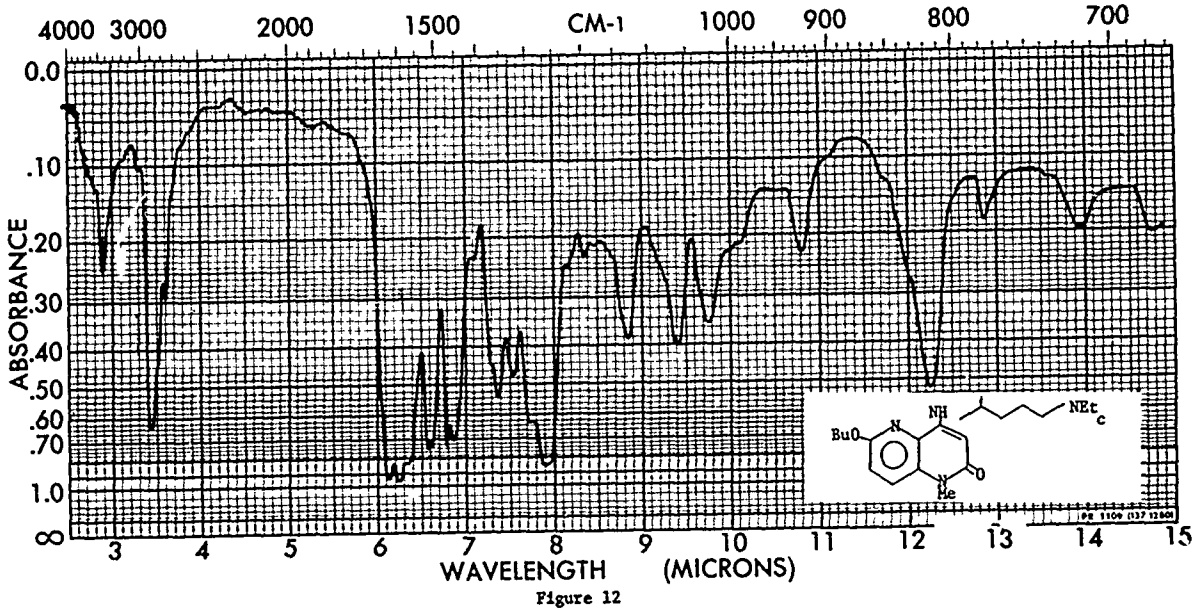


Figure 12

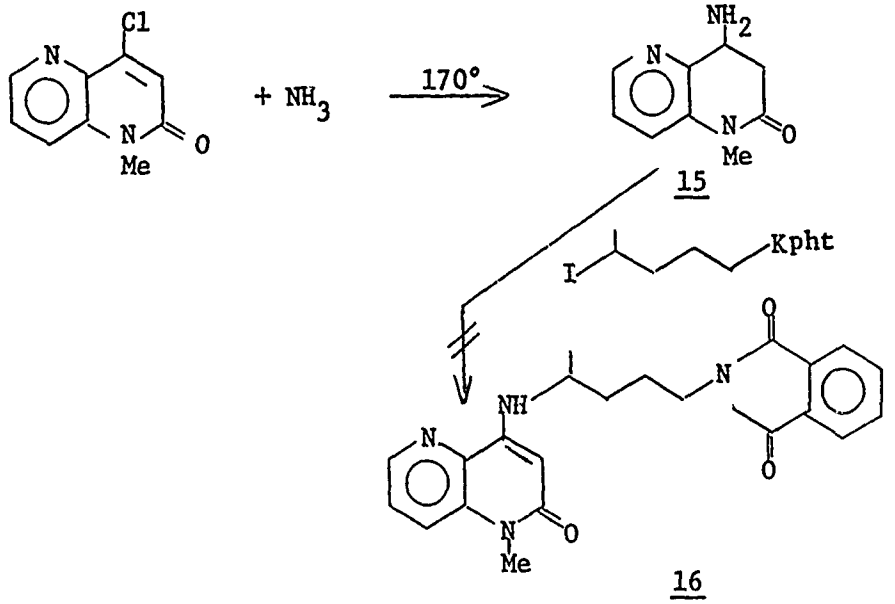
4.2.3 PRIMAQUINE SIDECHAIN

4-(4-Amino-1-methylbutylamino)-1,5-Naphthyridin-2-ones

Pentane-1,4-diamines, masked on either of the terminal amino groups, by a readily removable function, have not been reported. Thus, the introduction of the primaquine type sidechain into the naphthyridin-2-one nucleus required a radical departure from the sequence described in the previous two sections.

Our initial attempt to insert the primaquine type sidechain mimicked the technique currently employed to prepare both primaquine and quinocide derivatives. The sequence is shown in Scheme 3.

Scheme 3



The amination of 5 was effected in a glass pressure vessel to give 15 in 67% yield. Figure 13 represents the infrared spectrum of 15.

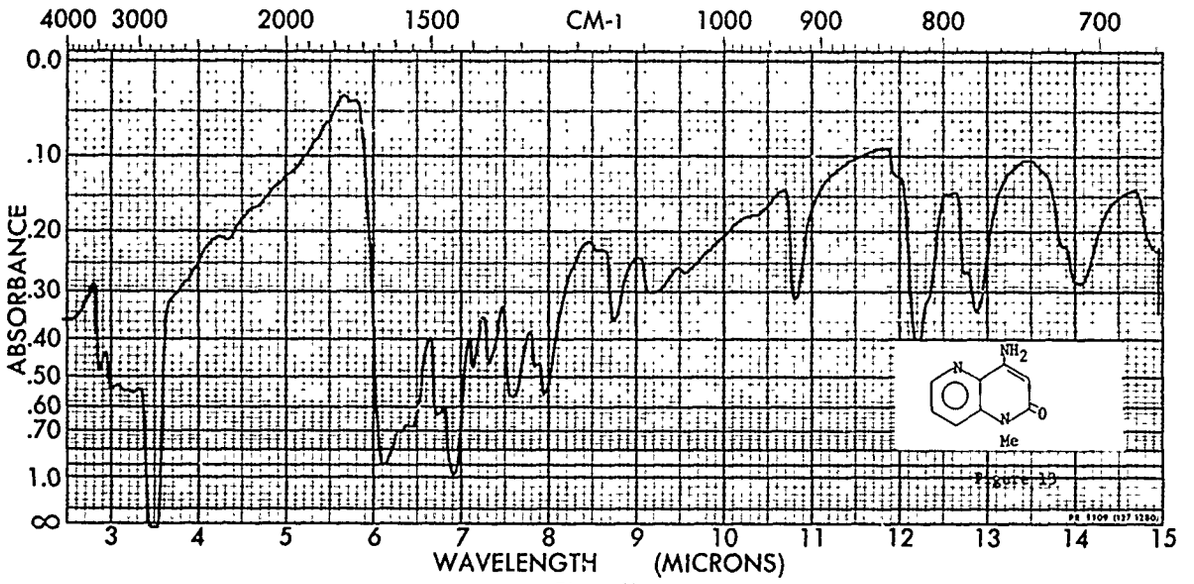
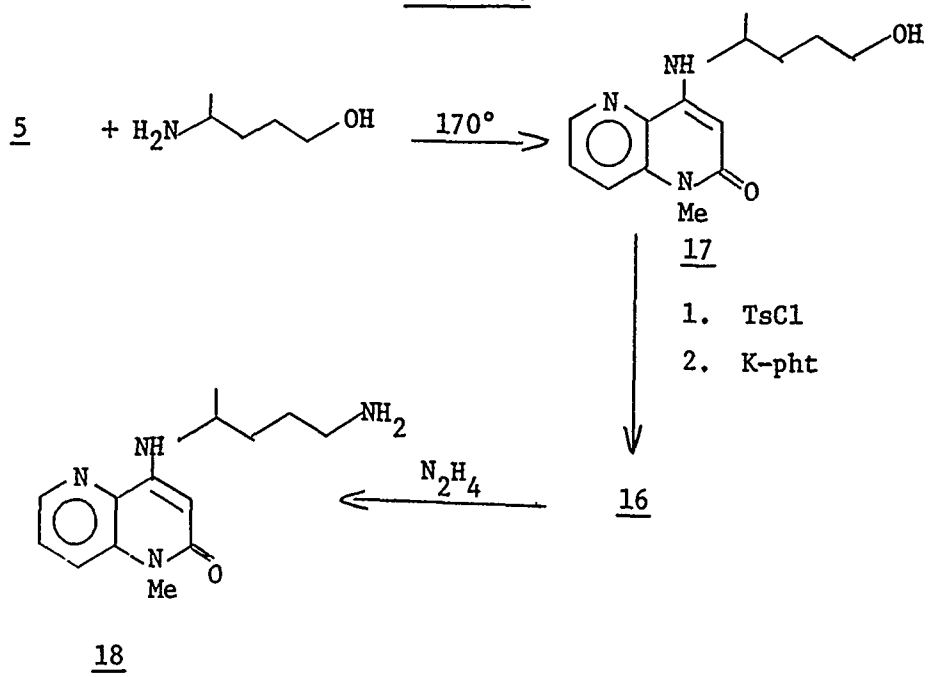


Figure 13

Attachment of the sidechain to yield 16 failed under a variety of experimental conditions. The alkylation of 15 with the isomeric and less sterically hindered iodoalkyl phthalimide also resulted in recovery of 15. Failure of 15 to undergo alkylation by iodoalkylphthalimides apparently is a reflection of the non-basicity of the 4-amino group.

Aza-primaquine could be prepared albiet, in low yield by adaption of the sequence of reaction developed by Carmack[9] for the preparation of primaquine. Scheme 4 summarizes this series of reactions.

Scheme 4



Amination of 5 with 4-amino-1-pentanol was quite facile, giving 17 (Figure 14) as a crystalline solid in 88% yield.

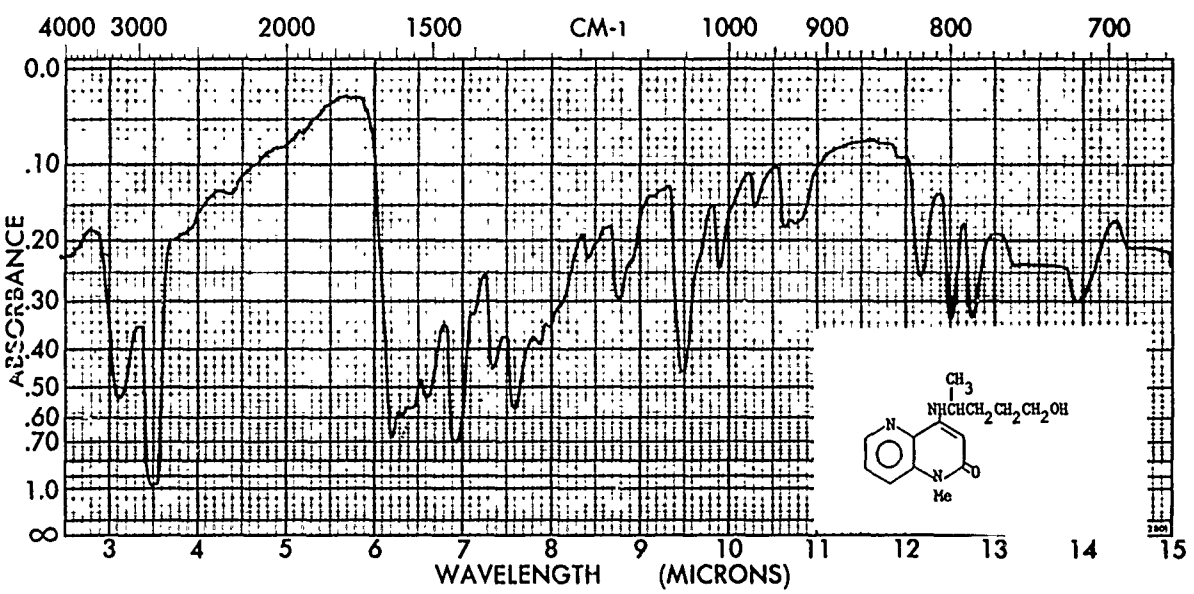
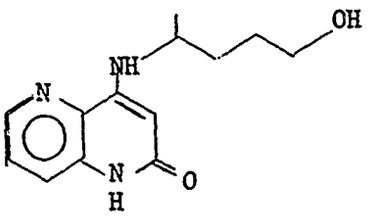
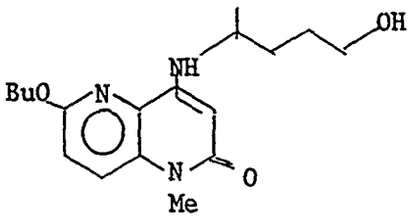


Figure 14

The synthons 4 and 12 were converted to 19 and 20 in comparable yields.

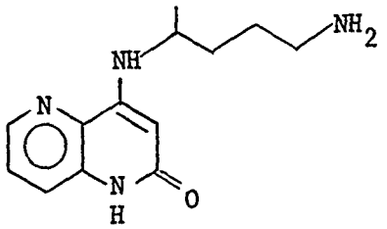


19

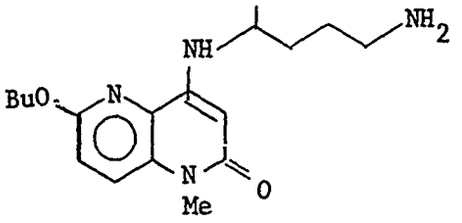


20

Tosylation of 17, 19, and 20 did not yield crystallizable materials. The identify of these materials was based on the anticipated changes in the infrared absorbances. The final two steps shown in Scheme 4 were carried out in standard fashion to yield the target compounds 18, 21, and 22 in low yield.



21



22

The aza-primaquine variants 18 and 21 were isolated as crystalline materials. Their infrared spectra are given in Figures 15-17, respectively.

The poor yield realized by the sequence illustrated in Scheme 4 made the need for a "masked" 1,4-pentanediamine painfully apparent. As was alluded to earlier in this section, no description of such molecules are recorded. New syntheses to "masked" 1,4-pentanediamines were developed and will be detailed in a later section. Scheme 5 illustrates the uses of a "masked" 1,4-pentanediamine for the introduction of the primaquine side-chain into the naphthyridinone ring system.

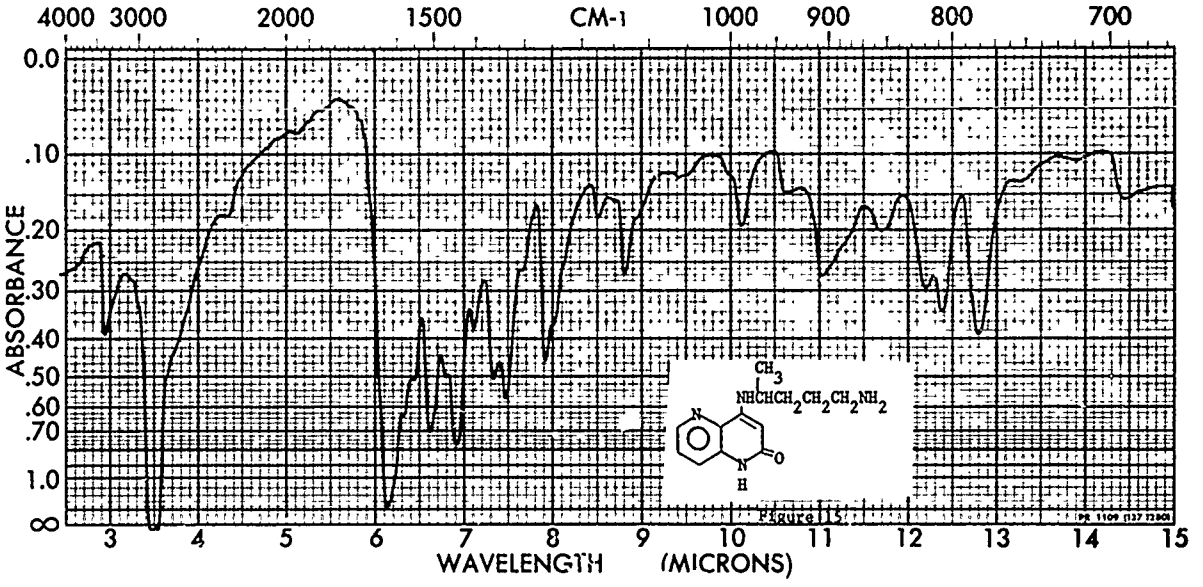


Figure 15

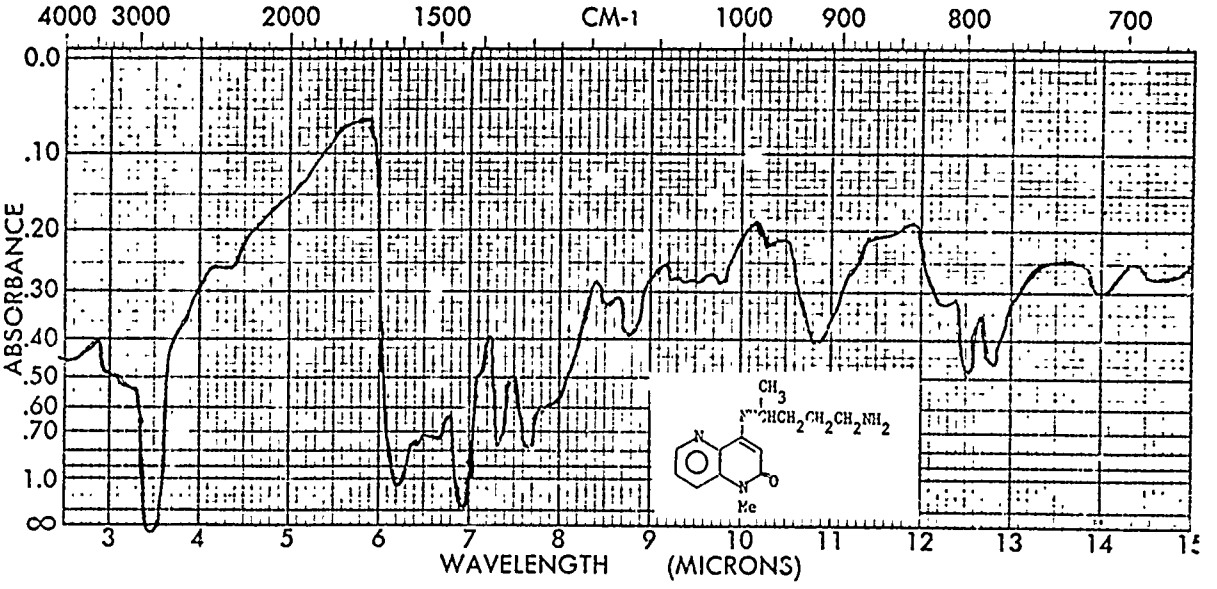


Figure 16

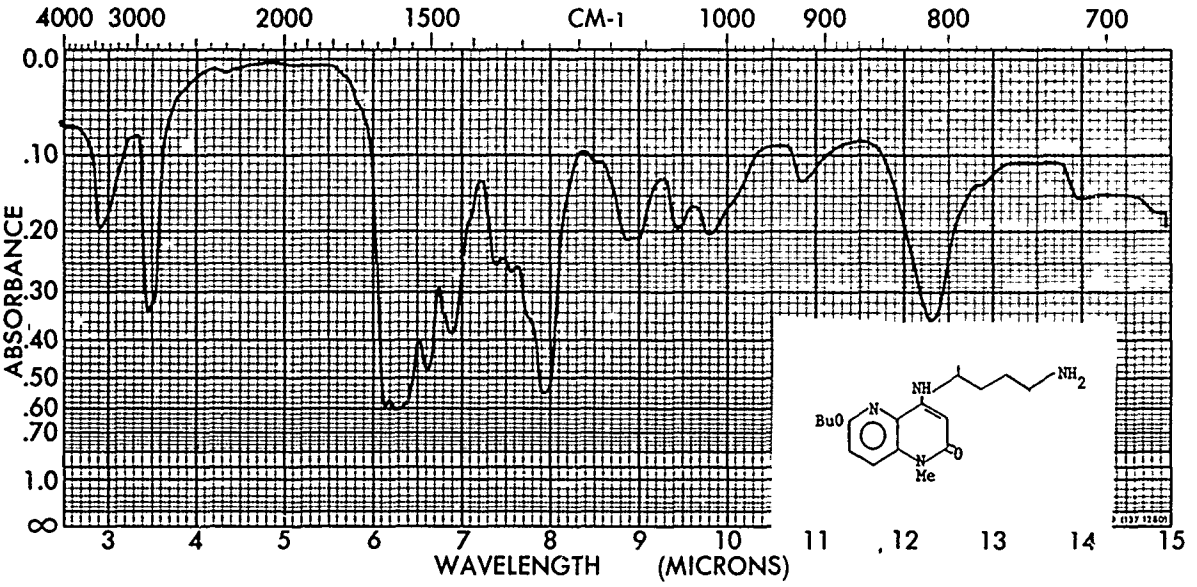
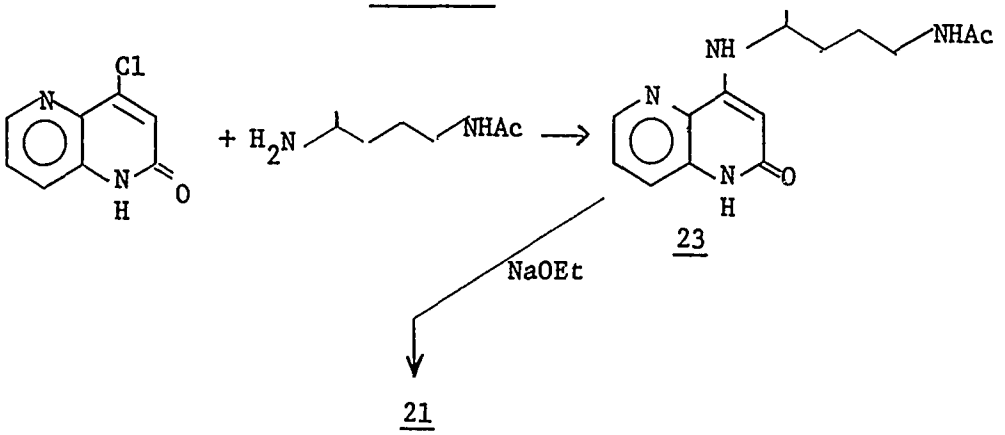


Figure 17

Scheme 5



Compound 23 was isolated as a crystalline solid in 57% yield. The infrared spectrum of 23 is given in Figure 18.

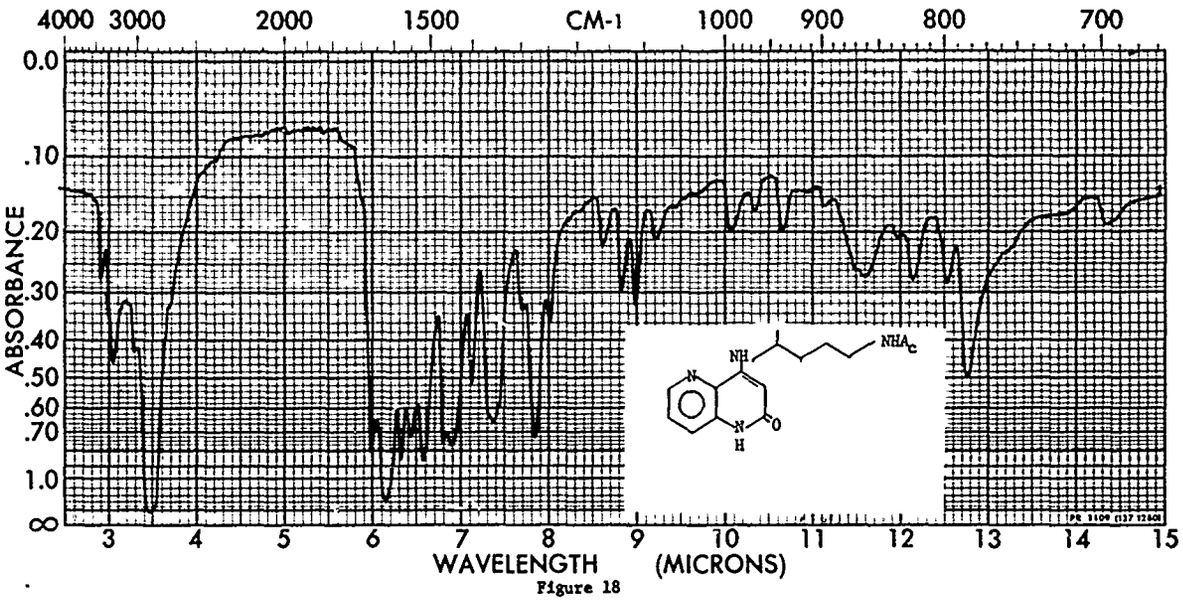
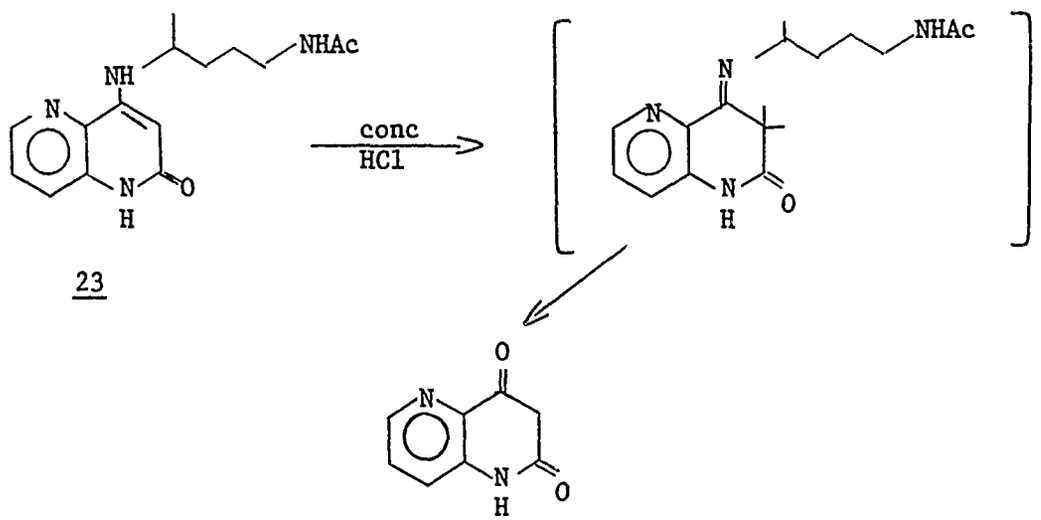


Figure 18

Deacetylation of 23 could be effected in ~60% yield with NaOEt/EtOH at 200°. Lower reaction temperatures or the use of Claisen's alkali failed to cleave the terminal amido group. Concentrated hydrochloric acid stripped the entire sidechain from the molecule.



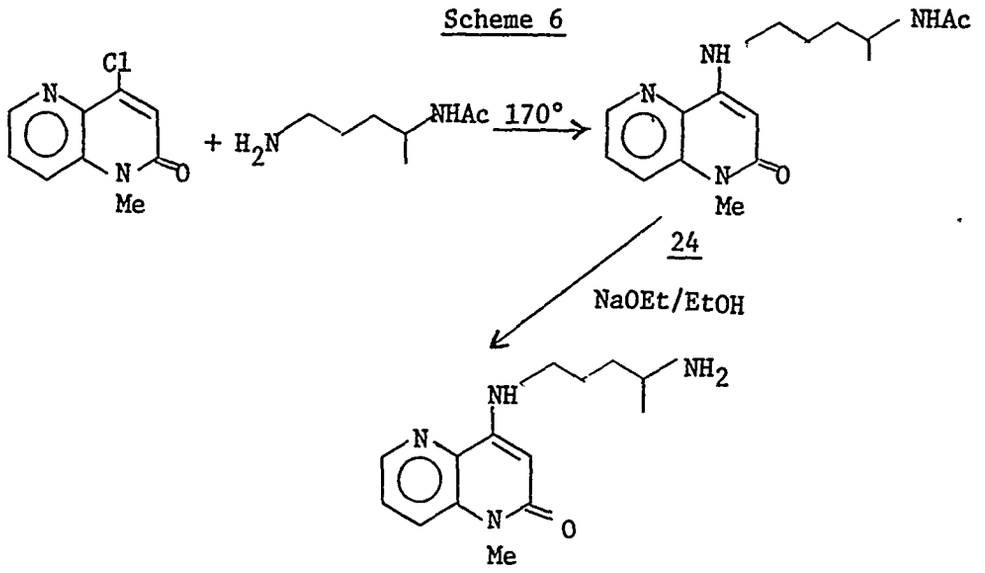
23

It is reasonable to assume a prototropic shift occurred to give the imino tautomer of 23, which then suffered destruction in the strong acid reaction environment.

4.2.4 QUINOCIDE CHAIN
4-(4-Amino-4-methylbutylamino)-1,5-Naphthyridin-2-ones

Attachment of diaminoalkanes, having a sidechain of the configuration found in the prophylactic drug quinocide, has been realized as outlined in Scheme 6.

Scheme 6



NT-37

Compound 24 was isolated in 83% as a white crystalline material. The nmr spectrum (Figure 19) shows the anticipated proton signals for the indicated

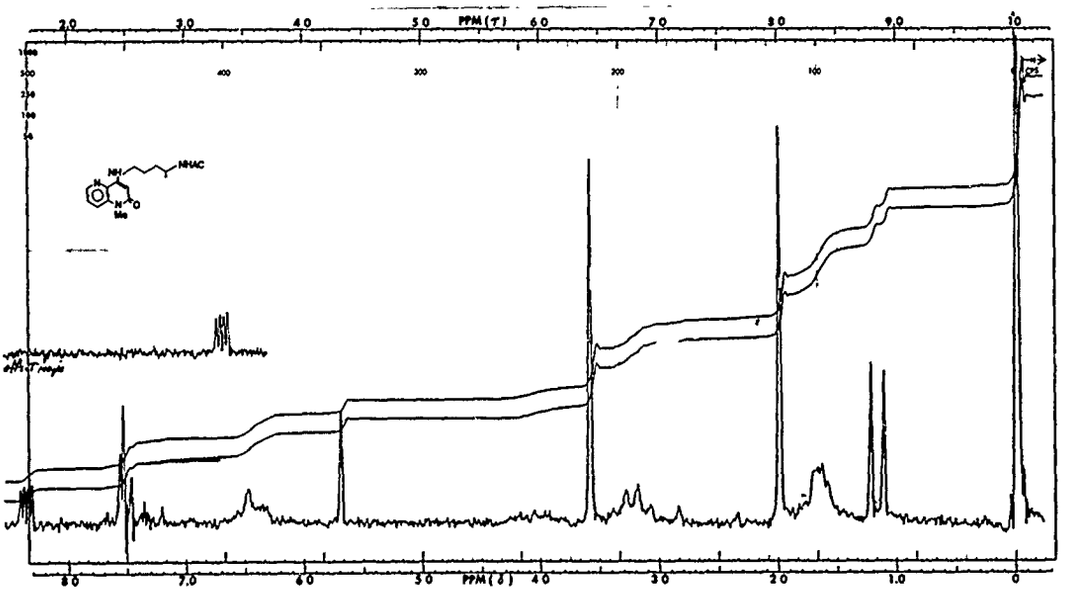
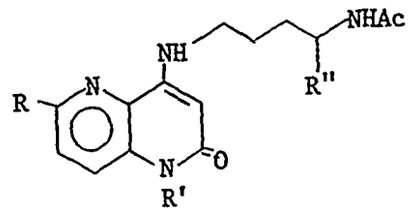


Figure 19

structure. Other derivatives of substituted "masked" quinocide type sidechains are listed in Table 2.

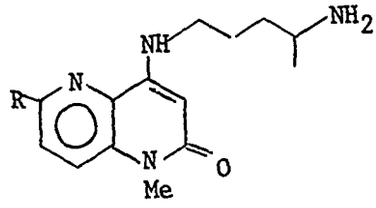
TABLE 2



No	R	R'	R''
NT-36	H	H	CH_3
NT-33	H	H	Et
NT-32	H	Me	Et
NT-35	BuO	Me	CH_3

Preparative yields for the variants listed in Table 2 ranged from 60-88%.

Deacetylation studies of the "Masked" quinocide type sidechains paralled those discussed for the isomeric primaquine type (Section 4.2.3). Use of NaOEt/EtOH at 200° cleaved the terminal amido function to yield the target drugs NT-37 and NT-38.



R = H (NT-37)

= BuO (NT-38)

Proton spectrum of NT-37 (Figure 20) clearly establishes that deacetylation was effected without the loss of the sidechain.

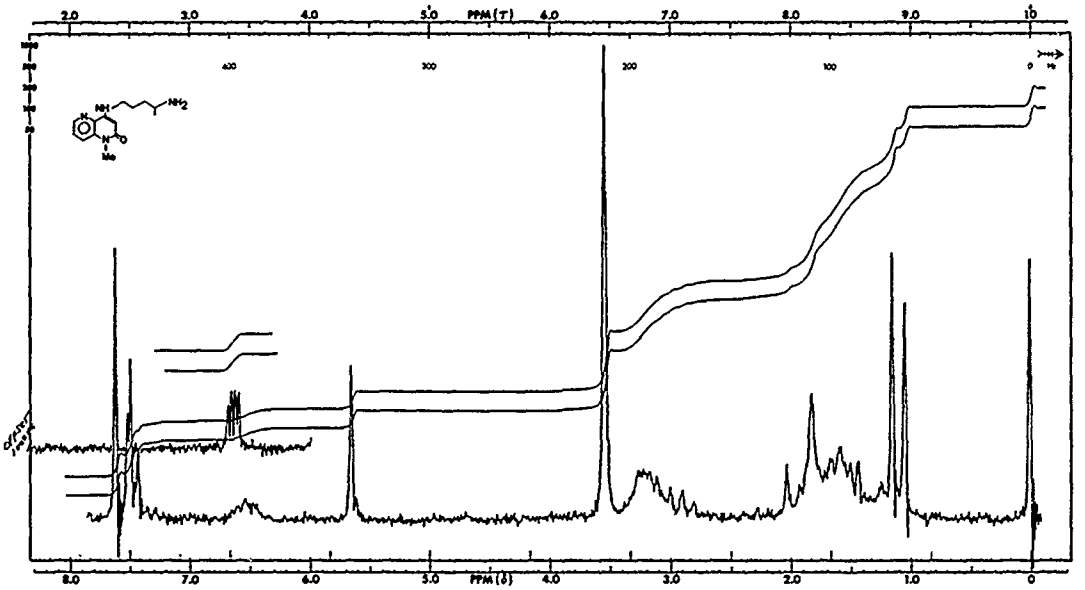


Figure 20

The infrared spectrum of NT-38, as the free base is given in Figure 21.

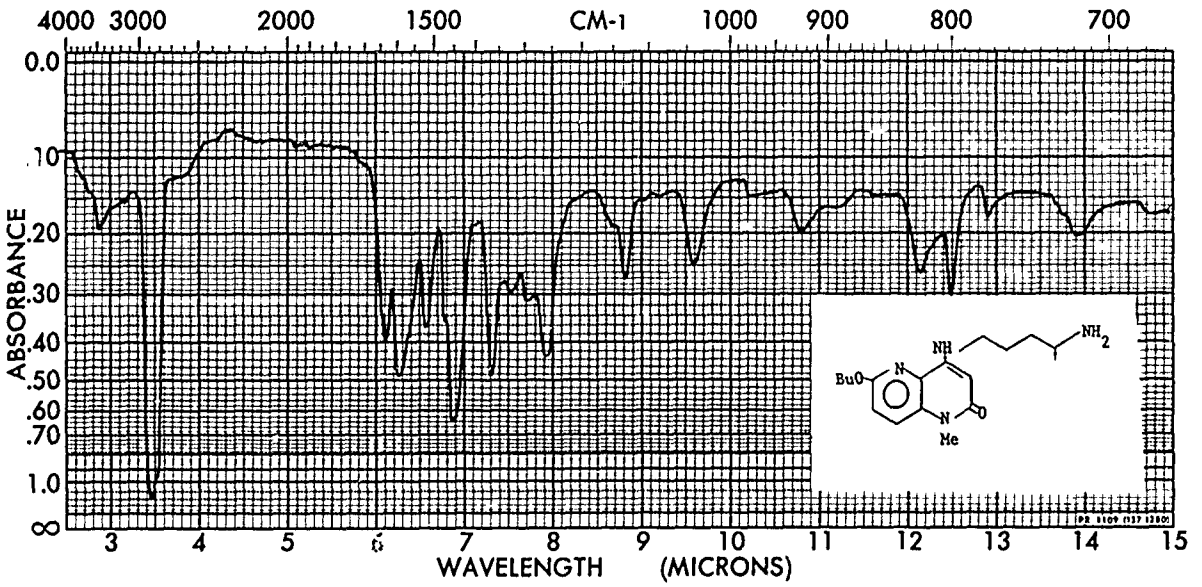
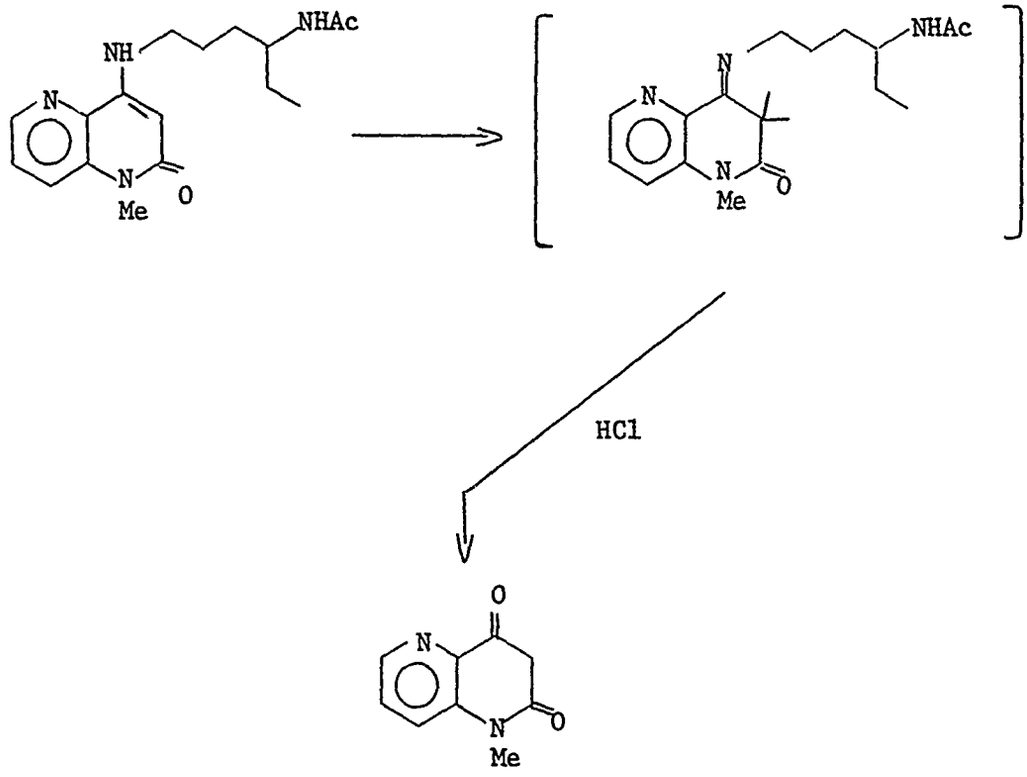
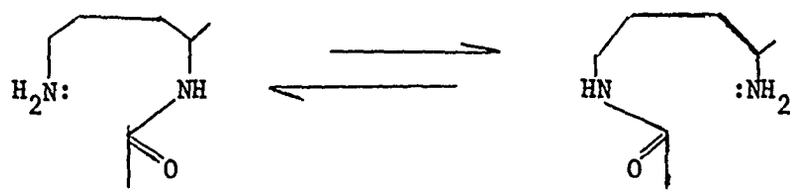


Figure 21

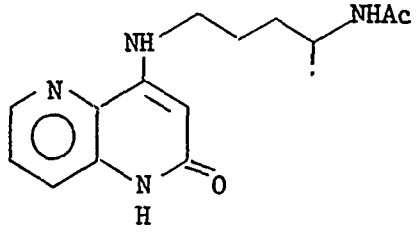
As discussed in the previous section, acid catalyzed cleavage of the terminal amido group also resulted in the loss of the sidechain in its entirety.



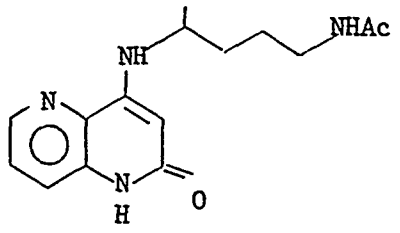
We considered the possibility that during the attachment of the isomeric "masked" 1,4-pentadiamines to the naphthyridinone nuclei an N → N acyl migration could occur. In this event the target naphthyridinones would not be substituted by the primaquine or quinocide type sidechains but only the sidechain dictated by the thermodynamics of the rearrangement.



It can be shown that this type of N → N acyl migration does not occur under the reaction conditions employed. The infrared spectra of the isomeric drugs NT-36 (Figure 22) and NT-41 (Figure 23) show distinctly different



NT-36



NT-41

absorption patterns.

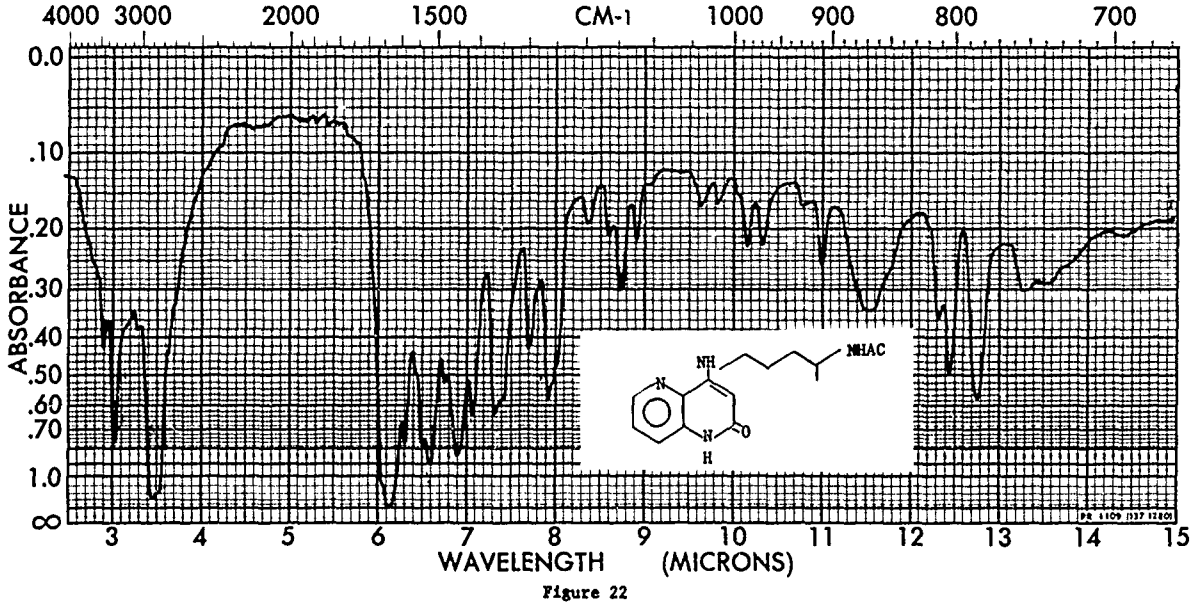


Figure 22

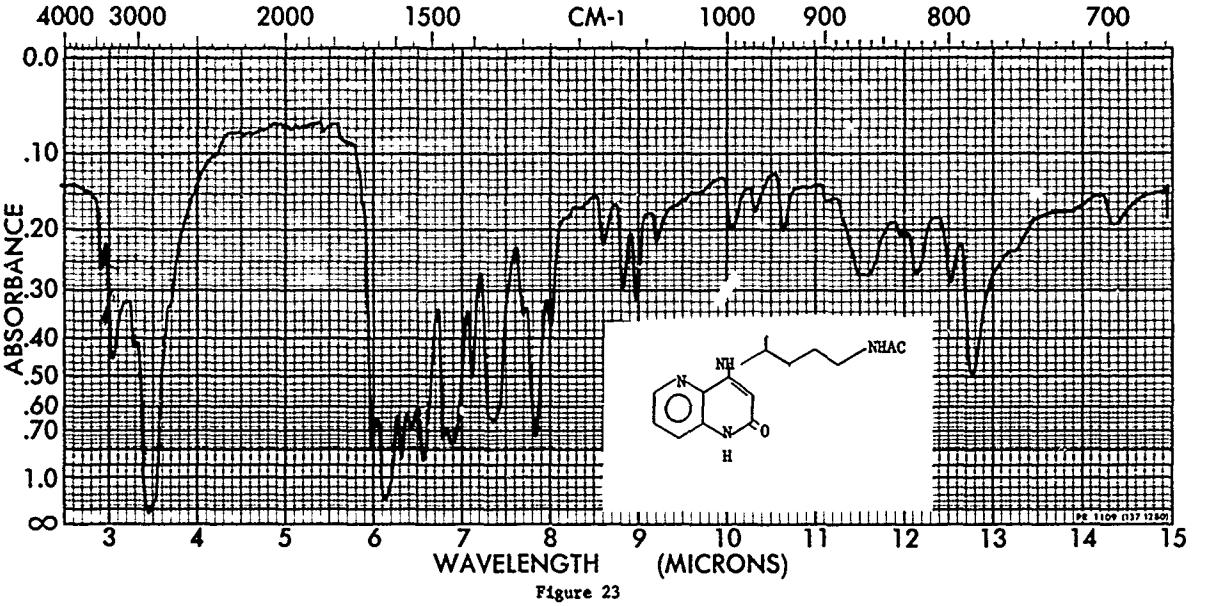


Figure 23

The structural distinction was further confirmed by a depression of the mixed melting point of the isomeric materials NT-36 and NT-41.

4.3 Sidechain Precursors

The "masked" 1,4-pentanediamines used to introduce primaquine and quinocide type sidechains into the naphthyridin-2-one were prepared according to the procedures appearing in Scheme 7.

Acetylation of 4-amino-1-pentanol is very facile, giving 25 as a distillable liquid in virtually quantitative yield. The direct conversion of the terminal hydroxy function to the phthalimido function was realized in >75% yield by adapting the procedure developed by Mitusunobu(10) to our particular molecule. The proton (Figure 24) and infrared spectra (Figure 25) of 26 clearly identify the terminal amide and imide groups.

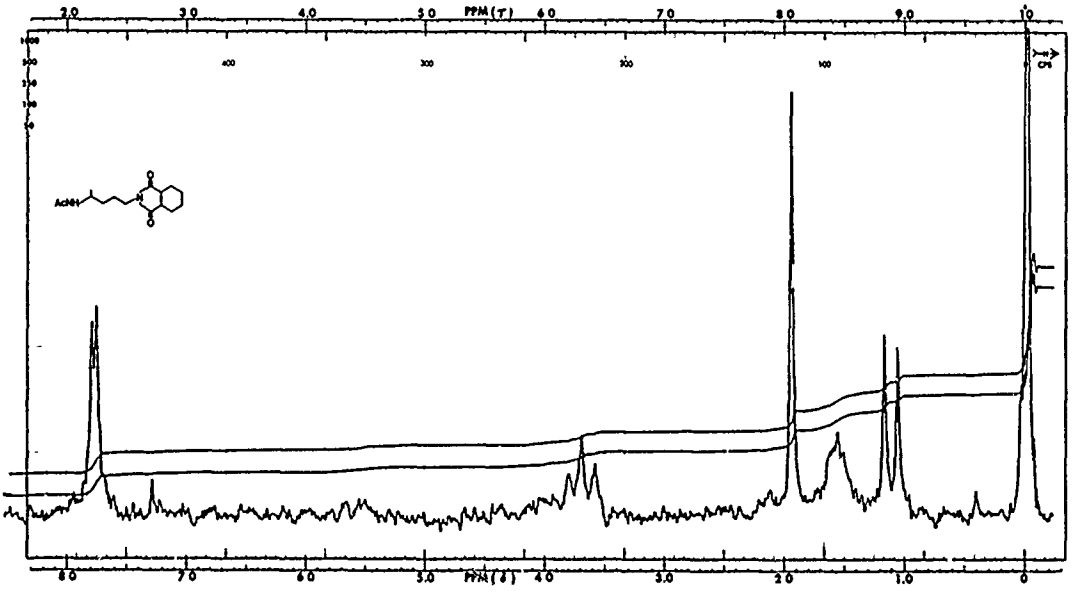
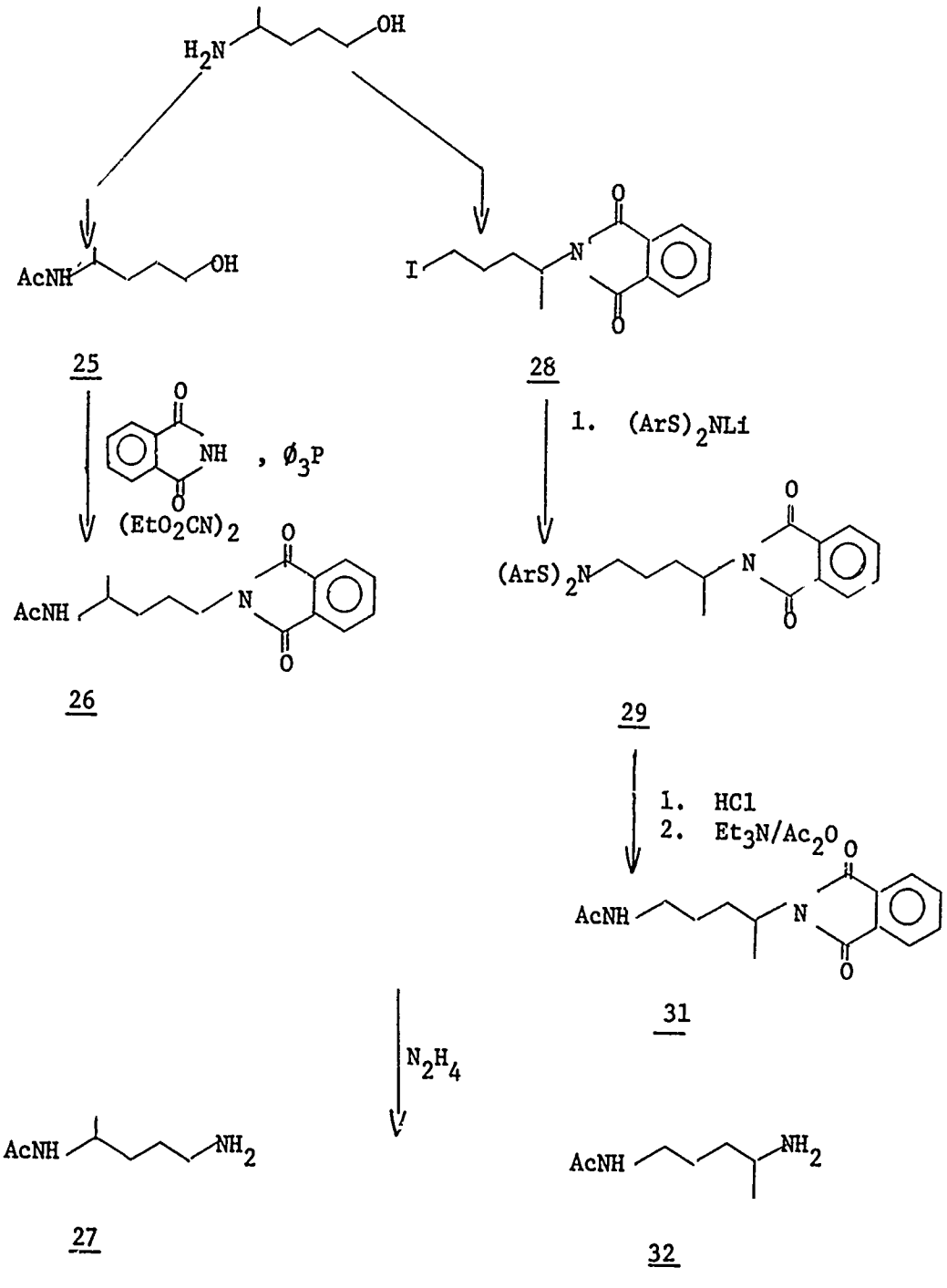


Figure 24

Scheme 7


H2N
OH
AcNH
OH
I
N
O
25
28
NH
, Ø3P
(EtO2CN)2
1. (ArS)2NLi
AcNH
N
(ArS)2N
26
29
1. HCl
2. Et3N/Ac2O
AcNH
N
31
N2H4
AcNH
NH2
AcNH
NH2
27
32

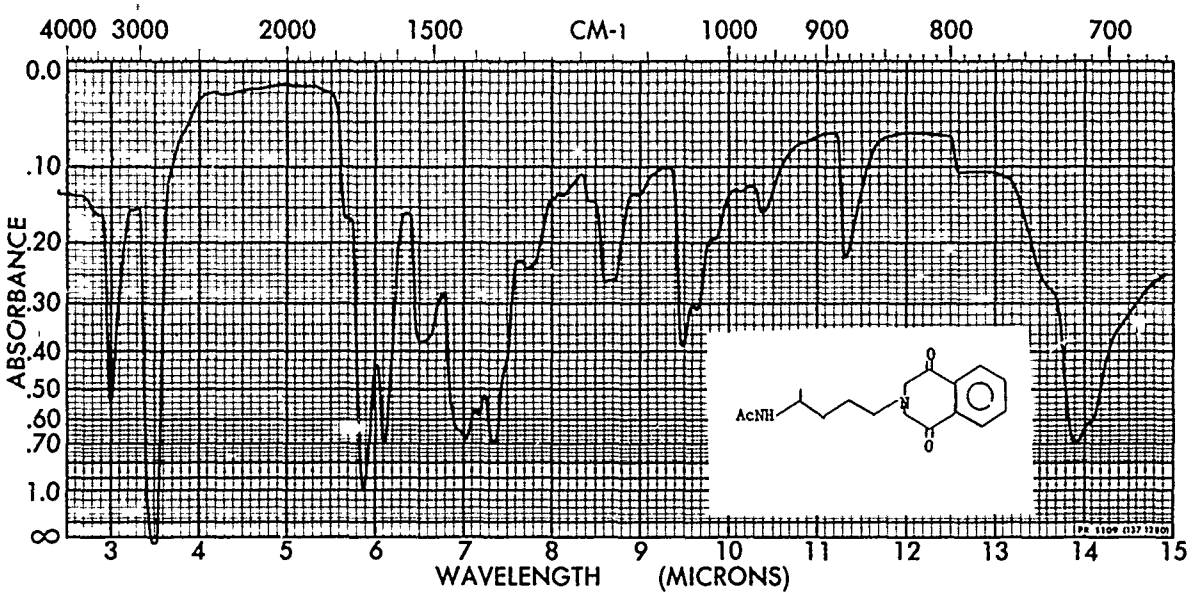
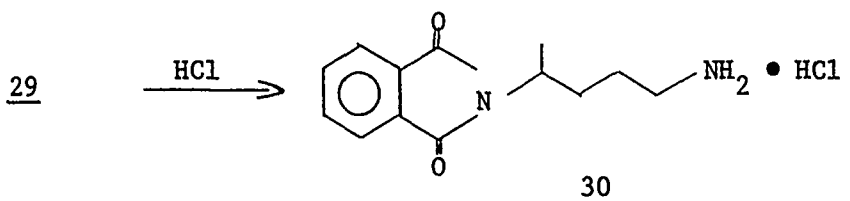


Figure 25

Formation of the sulfenamide 29 was accomplished in good yield by the Mukaiyama[11] technique for the selective transformation of terminal halogen to primary amines. The sulfenamide was readily cleaved by gaseous HCl yielding the corresponding amino alkyl phthalimide as the hydrochloride salt.



30

Attempts to isolate 30 as the free base resulted in loss of the phthalimido group. This facile intramolecular aminolysis of the phthalimido group has previously been observed by us and in other laboratories. Dissolution of 30 in acetic anhydride and gradual addition of Et_3N resulted in capture of the terminal amine function as it was released, to give the stable compound 31.

The standard technique for releasing the phthalimido blocking function gave the "masked" 1,4-pentanediamines 27 and 32. The proton spectra (Figures 26 and 27) clearly indicates that the series of transformations did not cause structural alteration of the carbon chain and that 27 and 32 are isomeric "masked" 1,4-pentanediamines.

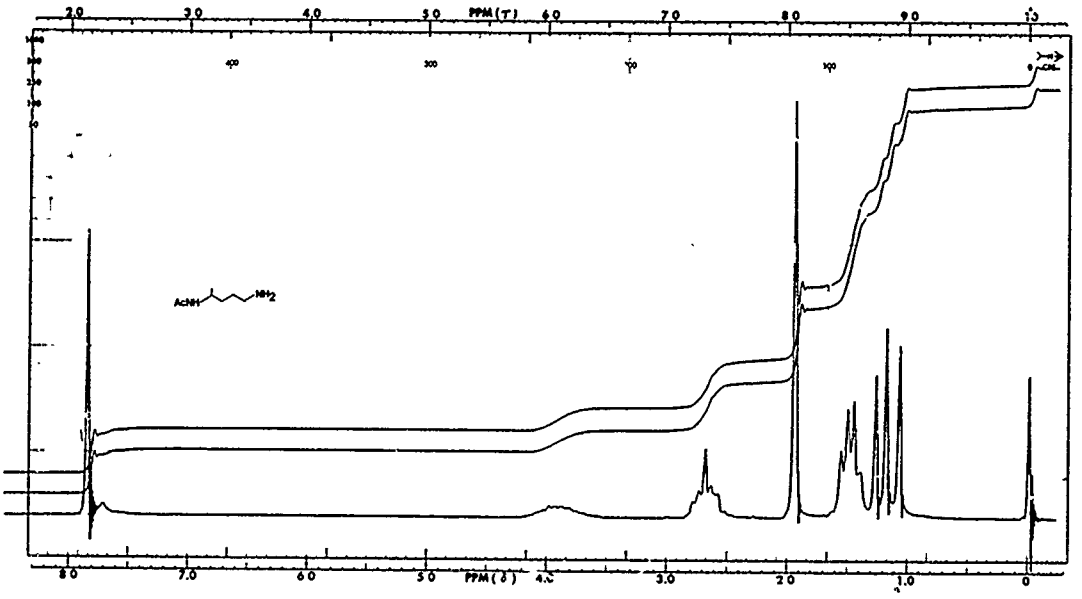


Figure 26

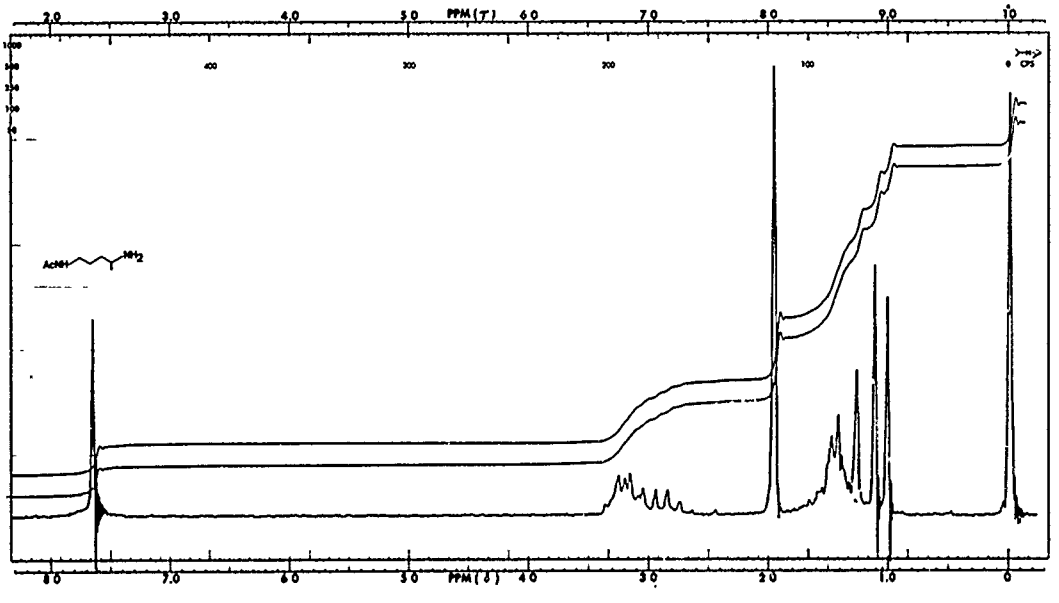
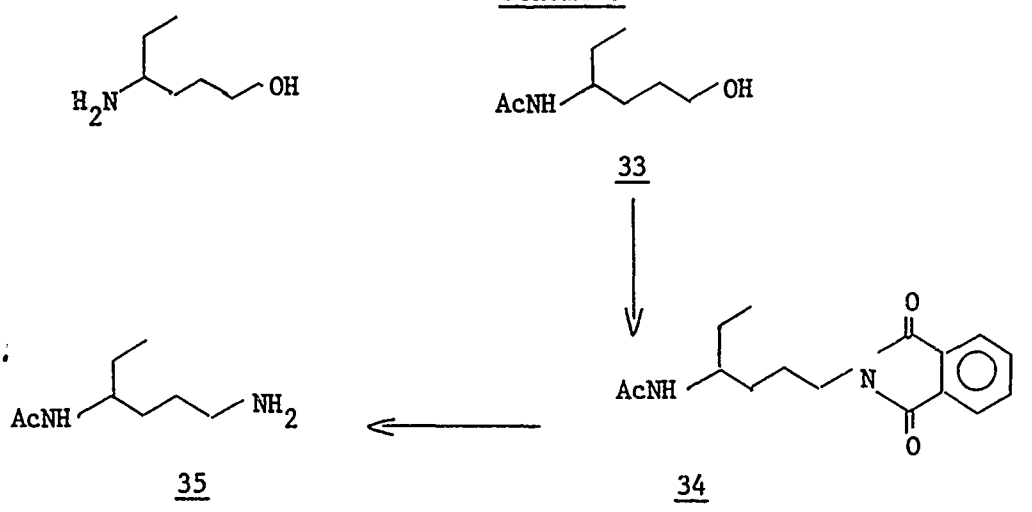


Figure 27

Particularly significant to distinguishing the isomeric structures are the chemical shift values for the CH-CH_3 group. Figure 26 shows the methyl resonance, α to the acetamido group, as a double and centered at δ 1.12. When this methyl group is α to the primary amine, as in compound 32, the doublet appears further upfield at δ 1.05.

A one carbon homolog of 27 was also synthesized by the sequence shown in Scheme 7. The particular intermediates in the conversion of 4-amino-1-hexanol to 35 are indicated in Scheme 8.

Scheme 8



The yields for the various steps shown were consistent with those found for preparation of compound 27. Infrared spectra of 34 and 35 are given in Figures 28 and 29, respectively.

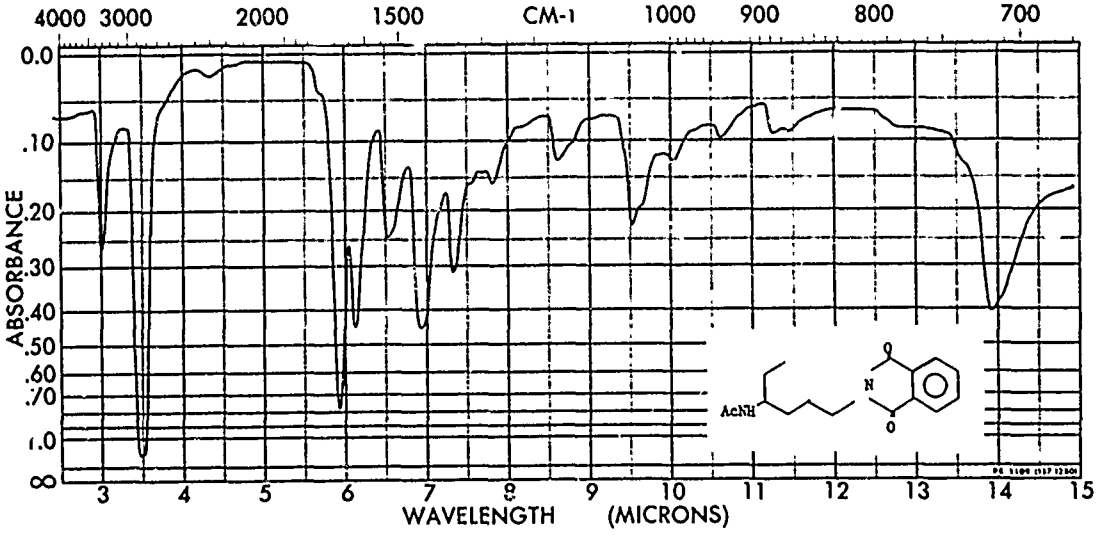


Figure 28

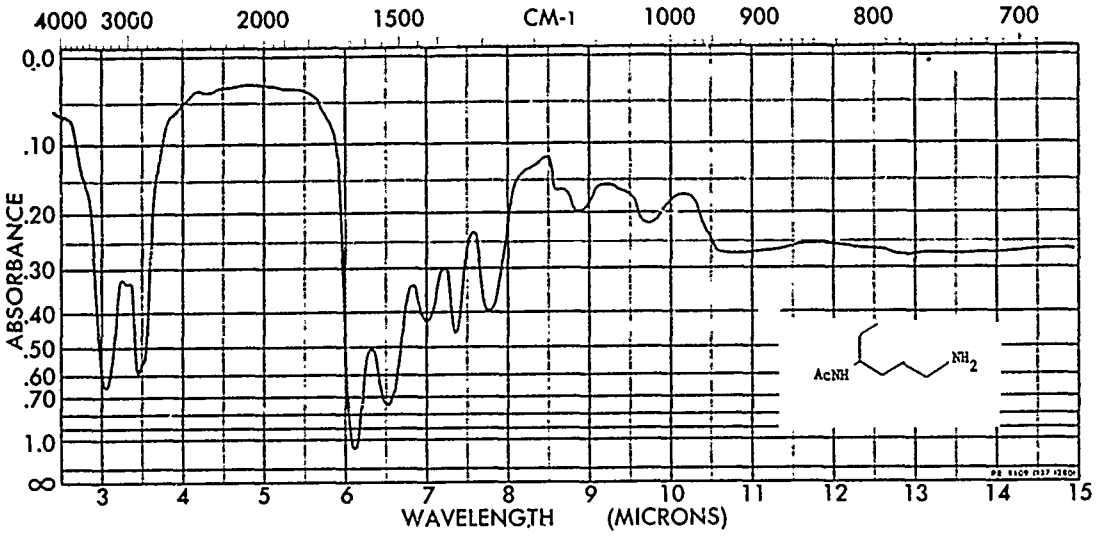
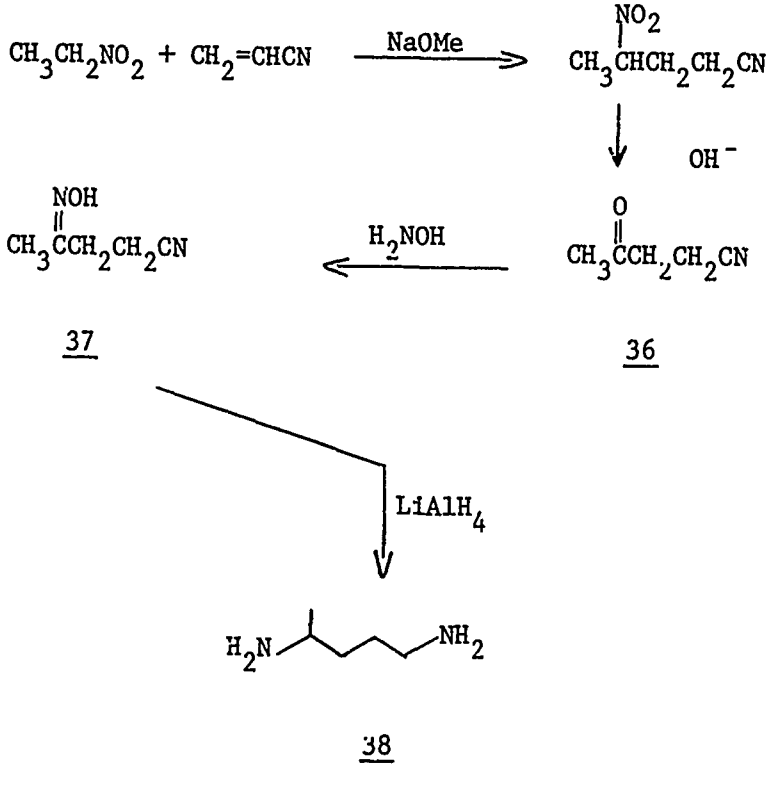


Figure 29

4.4 1,4-PENTANEDIAMINE

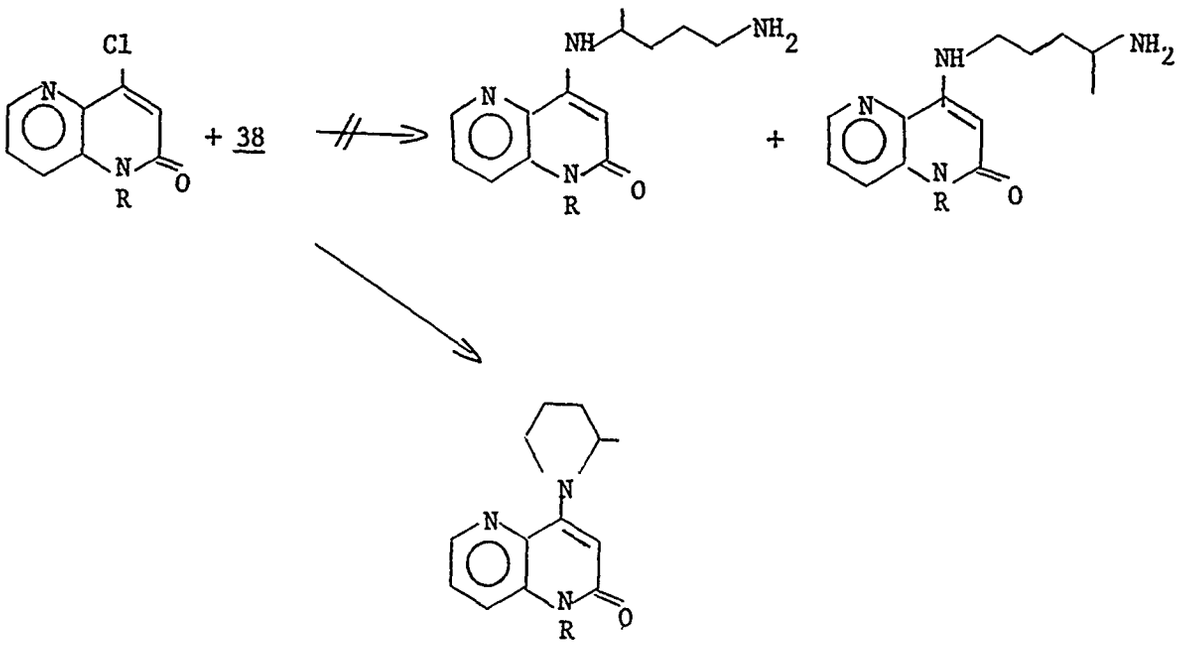
The diamine 38 was prepared as described by Vita.[12] Scheme 9 summarizes the reaction leading to 38.

Scheme 9



38

It was anticipated that the reaction of 38 with a 4-chloro-1,5-naphthyridin-2-one synthon might react preferentially at the unhindered primary amine termini, giving the quinocide type sidechain, or at least a separable mixture of the two isomeric sidechains.



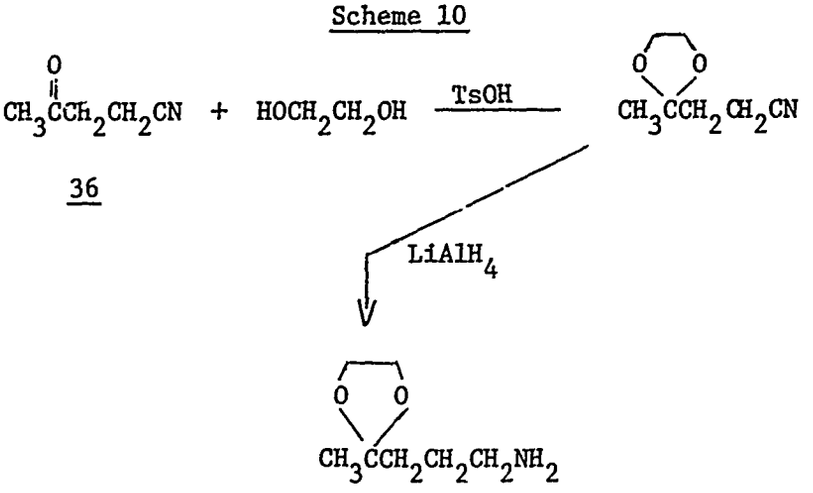
39

The product of this reaction was neither of the desired target structures. Although not completely characterized analysis of the reaction product appears to be consistent with 39. The structural assignment is in accord with the well known propensity of 1,4-pentanediamines and its congenors to cyclize to 2-methylpyrrolidine. Carmack[9] described an analogous cyclization to a 2-methylpyrrolidine derivative in the preparation of primaquine.

4.5 4-(1,3-DIOXOLANYL)-1-PENTYLAMINE

A route contemplated for the introduction of the quinocide chain into the naphthyridinone nucleus required the amine 40. Scheme 10 outlines the reaction leading to this intermediate.

Scheme 10



36

40

Masking the keto function of 36, as with the $LiAlH_4$ reduction, were realized by standard techniques.

5. EXPERIMENTAL

5.1 Target Drugs

5.1.1 Pentaquine Sidechain

4-(5-Isopropylaminopentylamino)-1,5-naphthyridin-2-one β-resorcylate (NT-7R)

A mixture of 4 g of 4-chloro-1,5-naphthyridin-2-one, 9.6 g of 5-isopropylamino-1-pentylamine, and 0.96 g of Cu/Bronze was heated, under N_2, at 175° for 18 hrs. After removal of excess amine, at reduced pressure, the residue was dissolved in $CHCl_3$ and dilute NaOH. The $CHCl_3$ layer was dried, evaporated, and the residued dissolved in THF and stirred for 1 hr. with a 2-3 molar excess of β-resorcyclic acid. The precipitate was filtered, washed with large volumes of Et_2O and recrystallized from MeOH/Et_2O, mp = 147-150°.

Anal calcd for $C_{23}H_{30}N_4O_5$; %C, 62.44: %H, 6.79: %N, 12.79; Found: %C, 61.93; %H, 7.00; %N, 12.23

6-Butoxy-4-(5-isopropylaminopentylamino)-1-methyl 1,5-naphthyridin-2-one β-resorcylate (NT-30)

A mixture of 1.6 g of 6-butoxy-4-chloro-1-methyl-1,5-naphthyridin-2-one, 2.6 g of 5-isopropylaminopentylamine, and 0.2 g of Cu/Bronze was heated at 170° for 18 hours, under N_2. After the excess amine was distilled, the residue was dissolved in $CHCl_3$ and washed with dilute aqueous Na_2CO_3. The $CHCl_3$ was evaporated and the residue dissolved in 150 ml of hexane, charcoal treated, filtered, and the C_6 evaporated. The thick residue gradually solidified, mp 53° (C_6).

Anal calcd for $C_{21}H_{34}N_4O_2$: %C, 67.38: %H, 9.09; %N, 14.97 Found: %C, 67.32; %H, 9.08; %N, 15.18

The above material was dissolved in either and reacted with three equivalents of β-resorcylic acid. The precipitated solid was filtered, washed with ether, and recrystallized from EtOH, mp 177-9° (melting with evolution of EtOH at ∿110°).

Anal calcd for $C_{28}H_{40}O_6 \cdot C_2H_5OH$: %C, 62.71: %H, 8.01; %N, 9.75: Found: %C, 63.01; %H, 8.40; %N, 10.00

5-Hydroxy-4-(5-isopropylaminopentylamino)-1-methyl-1,5-naphthyridin-2-one dihydrochloride (NT-31)

NT-30 was dissolved in concentrated HCl and heated on a steambath overnight. The reaction was evaporated to dryness and the residue recrystallized from Et_2O/EtOH, mp = 275-7°.

Anal calcd for $C_{17}H_{28}Cl_2N_4O_2 \cdot 1/2\ H_2O$: %C, 51.13; %H, 7.27; %N, 14.06: Found: %C, 51.59; %H, 6.77; %N, 13.83

5-Hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridin-2-one hydrochloride hydrate (NT-39)

A mixture of 1.96 g of 4-chloro-1,5-naphthyridin-2,6-dione and 5.7 g of 5-isopropylamino-1-pentylamine was heated at 170° for 1 hr. The reaction was extracted with hot ether, dissolved in ethanol, and filtered. The ethanol solution was saturated with gaseous HCl and concentrated. The product was precipitated with ether and recrystallized from aqueous ethanol, mp >300.

Anal calcd for $C_{16}H_{27}ClN_4O_3$: %C, 53.63; %H, 7.54; %N, 15.64 Found: %C, 53.53; %H, 7.68; %N, 15.88

5.1.2 Pamaquine Sidechain

4-(4-Diethylamino-1-methylbutylamino)-1-methyl-1,5-naphthyridin-2-one di-β-resorcylate (NT-27)

A mixture of 2.5 g of 4-chloro-1-methyl-1,5-naphthyridin-2-one, 6.1 g of 2-amino-5-diethylaminopentane, and 0.25 g of copper/bronze was heated, under N_2, at 170° for 20 hrs. After removal of excess amine, at reduced pressure, the residue was dissolved in $CHCl_3$ and extracted with aqueous Na_2CO_3. NT-27, as the free base, was isolated as a pale yellow oil, bp = 203-210°/0.08 mm, yield 2.73 g.

The above was dissolved in 50 ml of ether and added to 10 g of resorcylic acid in 300 ml of ether. The precipitate solid was filtered and washed with large volumes of ether, mp = 60-65° (softening).

Anal calcd for $C_{32}H_{40}N_4O_8$: %C, 63.16; %H, 6.58; %N, 9.21: Found: %C, 63.85%; %H, 6.86; %N, 9.63

6-Butoxy-(4-diethylamino-1-methylbutylamino)-1-methyl-1,5-naphthyridin-2-one (NT-40)

In the manner described above, 6-butoxy-4-chloro-1-methyl-1,5-naphthyridin-2-one was converted to the titled compound. NT-40, as the free base, was isolated as a viscous yellow oil, $b_{0.1m}$ = 210-215, in 75% yield.

5.1.3 Primaquine Sidechain

4-(4-Amino-1-methylbutylamino)-1-methyl-1,5-naphthyridin-2-one di-β-resorcylate (NT-28)

A mixture of 7.71 g of 4-chloro-1-methyl-1,5-naphthyridin-2-one, 12.4 g of 4-amino-1-pentanol, and 0.8 g of Cu/Bronze was heated at 170° for 20 hrs. The excess amine was distilled and the residue dissolved in 200 ml of $CHCl_3$ and 100 ml of dilute aqueous Na_2CO_3. The $CHCl_3$ was evaporated and the residue stirred with 100 ml of ether. The product, 4-(4-hydroxy-1-methylbutylamino)1-methyl-1,5-naphthyridin-2-one (662-15), was filtered and recrystallized from H_2O, mp = 149-151°, yield 88%.

Anal calcd for $C_{14}H_{19}N_3O_2$: %C, 64.37; %H, 7.28;
%N, 16.09: Found: %C, 64.76; %H, 7.36;
%N, 16.27

A solution of 2.85 g of tosyl chloride in 25 ml of ether was added dropwise to a cold $CHCl_3$ solution of 2.61 g of 662-15. After stirring at ambient temperature overnight, the solvents were removed at reduced pressure and the residue added to water and extracted with $CHCl_3$. The tosylate was isolated as a thick oil. Without further purification the tosylate was dissolved in 60 ml of DMF and refluxed for 3 hours with 2 g of potassium phthalimide. The cooled reaction was diluted with three volumes of water and extracted with $CHCl_3$. The semi-solid $CHCl_3$ residue was stirred with ether, filtered, and recrystallized from heptane/benzene, mp = 178-180°.

The above phthalimido derivative was refluxed with three equivalents of hydrazine in ethanol for 3 hours. The reaction was evaporated to dryness, under reduced pressure, and the residue extracted several times with hot benzene. The benzene was evaporated and residue tritrated with ether, filtered, and recrystallized from heptane, mp = 95-6°.

Anal calcd for $C_{14}H_{20}N_4O$: %C, 64.62; %H, 7.69;
%N, 21.56: Found: %C, 64.22; %H, 7.81;
%N, 21.99

NT-28 was dissolved in a minimum amount of THF and reacted with three equivalents of resorcylic acid in THF. After one hour the reaction was concentrated and added to a large volume of ether. The precipitated solid was filtered and washed with ether, mp 115-119° (softening).

Anal calcd for $C_{28}H_{32}N_4O_9$: %C, 59.15; %H, 5.64;
%N, 9.85: Found: %C, 58.85; %H, 5.59;
%N, 10.09

4-(4-Amino-1-methylbutylamino)-6-butoxy-1-methyl-1,5-naphthyridin-2-one di-β-resorcylate (NT-42)

In the manner described above, 6-butoxy-4-(4-hydroxy-1-butylamino)-1-methyl-1,5-naphthyridin-2-one was isolated in 79% yield from 6-butoxy-4-chloro-1-methyl-1,5-naphthyridin-2-one and 4-amino-1-pentanol, mp 85-6°.

Anal calcd for $C_{18}H_{27}N_3O_3$: %C, 64.86; %H, 8.11; %N, 12.61: Found: %C, 64.99; %H, 8.09; %N, 13.23

The above material was reacted sequentially with tosyl chloride, potassium phthalimide, and hydrazine as detailed for the preparation of NT-28. The product, a viscous oil, was converted to the β-resorcylate in the usual manner, mp 118-120 (Et_2O/EtOH).

Anal calcd for $C_{27}H_{40}N_4O_7$: %C, 60.90; %H, 7.50; %N, 10.53: Found: %C, 60.44; %H, 6.98; %N, 10.99

4-(4-Acetamido-1-methylbutylamino)-1,5-naphthyridin-2-one (NT-41)

Two equivalents of 5-acetamido-2-pentylamine were heated at 170° for 18 hours with 4-chloro-1,5-naphthyridin-2-one. The reaction was dissolved in chloroform, extracted with water, dried, and evaporated to dryness. The viscous residue solidified when stirred with warm acetone, yield 57%, mp 174-5°.

Anal calcd for $C_{15}H_{20}N_4O_2$: %C, 62.50; %H, 6.94; %N, 19.44: Found: %C, 62.66; %H, 6.92; %N, 19.81

4-(4-Amino-1-methylbutylamino)-1,5-naphthyridin-2-one (NT-29)

A freshly prepared NaOEt solution (0.3 g Na/30 ml EtOH) containing 1.3 g of NT-41 was heated at 200° for 17 hours in a glass pressure vessel. After evaporation of the solvent, the residue was dissolved in water and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ and recrystallization from toluene yielded 0.6 g of product, mp 193-5°.

Anal calcd for $C_{13}H_{18}N_4O$: %C, 63.41; %H, 7.32; %N, 22.76: Found: %C, 63.00; %H, 7.46; %N, 22.39

5.1.4 Quinocide Sidechain

4-(4-Acetamindo-1-pentylamino)-1,5-naphthyridin-2-one (NT-36)

Two molar equivalents of 4-acetamido-1-pentylamine were heated at 170° for 18 hours with 4-chloro-1,5-naphthyridin-2-one. The reaction was dissolved in $CHCl_3$, extracted with water, dried, and evaporated. The viscous residue gradually crystallized when stirred with ether, yield 58%, mp, 186-7° (acetone).

Anal calcd for $C_{15}H_{20}N_4O_4$: %C, 62.50; %H, 6.94; %N, 19.44: Found: %C, 62.38; %H, 7.01; %N, 18.92

4-(4-Acetamido-1-pentylamino)-1-methyl-1,5-naphthyridin-2-one (NT-34)

In a similar manner, 4-chloro-1-methyl-1,5-naphthyridin-2-one was converted to the titled compound in 83% yield, mp 139-140° ($PhCH_3$).

Anal calcd for $C_{16}H_{22}N_4O_2$: %C, 63.58; %H, 7.28; %N, 18.54: Found: %C, 63.25; %H, 7.32; %N, 18.44

4-(4-Amino-1-pentylamino)-1-methyl-1,5-naphthyridin-2-one β-resorcylate (NT-37)

A NaOEt/EtOH solution, 35 ml, containing 3 g of NT-34 was heated at 200° for 17 hours in a glass pressure vessel. The solvent was evaporated and the residue dissolved in water and extracted with $CHCl_3$. After evaporation of the $CHCl_3$ the residue was dissolved in THF and reacted with three equivalents of β-resorcylic acid. The THF was evaporated and the residue extracted several times with hot Et_2O and recrystallized from Et_2O/EtOH, mp 144-6°, yield 65%.

Anal calcd for $C_{21}H_{26}N_4O_5$: %C, 60.87; %H, 6.28; %N, 13.53: Found: %C, 60.33; %H, 6.68; %N, 13.44

4-(4-Acetamido-1-pentylamino)-6-butoxy-1-methyl-1,5-naphthyridin-2-one (NT-35)

6-Butoxy-4-chloro-1,5-naphthyridin-2-one was converted to the titled compound in 78% yield as described above, mp 151-3° ($PhCH_3$).

Anal calcd for $C_{20}H_{30}N_4O_3$: %C, 64.17; %H, 8.02; %N, 14.97: Found: %C, 64.39; %H, 8.06; %N, 15.11

4-(4-Amino-1-pentylamino)-6-butoxy-1-methyl-1,5-naphthyridin-2-one di-β-resorcylate (NT-38)

NT-35 was reacted with NaOEt as described for the preparation of NT-37. The titled compound was isolated in 80% yield, as the free base, mp 93-4° ($PhCH_3/C_6$).

The purified free base in THF was treated with three equivalents of β-resorcylic acid. The THF was evaporated and the solid residue extracted several times with hot ether, mp 105-9° (softening).

Anal calcd for $C_{32}H_{40}N_4O_{10}$: %C, 60.00; %H, 6.25; %N, 8.75: Found: %C, 59.62; %H, 6.67; %N, 9.00

4-(4-Acetamido-1-hexylamino)-1-methyl-1,5-naphthyridin-2-one (NT-32)

4-Chloro-1-methyl-1,5-naphthyridin-2-one reacted with two equivalents of 4-acetamido-1-hexylamine gave the titled compound in 80% yield, mp 157-8 (PhH/hexane).

Anal calcd for $C_{17}H_{24}N_4O_2$: %C, 64.56; %H, 7.59: %N, 17.72: Found: %C, 65.01; %H, 7.55; %N, 18.01

4-(4-Acetamido-1-hexylamino)-1,5-naphthyridin-2-one (NT-33)

The titled compound was prepared from 4-chloro-1,5-naphthyridin-2-one as described above in 60% yield, mp 191-2° (H_2O).

Anal calcd for $C_{16}H_{22}N_4O_2$: %C, 63.58; %H, 7.28; %N, 8.54: Found: %C, 63.55; %H, 7.35; %N, 18.15

5.2 Naphthyridinone Synthons

4-Chloro-1,5-naphthyridin-2-one (662-1)

2,4-Dichloro-1,5-naphthyridine, 27.2 g, in 272 ml of 6N HCl and 272 ml of dioxane was heated at reflux for 3 hours. Decolorizing charcoal was added and the solution filtered hot. The reaction was cooled overnight and filtered. The filtercake was added to a dilute $NaHCO_3$ solution, stirred, and filtered. Yield was 17.4 g. Neutralization of the original aqueous filtrate with Na_2CO_3 and cooling for several days yielded an additional 3.6 g of product.

4-Chloro-1-methyl-1,5-naphthyridinium fluoro-sulfonate (655-91)

A solution of 10.1 g of fluoromethylsulfonate in 10 ml of CH_2Cl_2 was added dropwise to 13.3 g of 4-chloro-1,5-naphthyridine in 150 ml of CH_2Cl_2 cooled to 15°. The reaction was stirred an additional 0.5 hrs, filtered, and the filtercake washed with ether. Yield 21.4 g (95%), mp 145-150° (dec).

4-Chloro-1-methyl-1,5-naphthyridin-2-one (655-92)

Solutions of 88.5 g of potassium ferricyanide in 400 ml of H_2O and 30.8 g of sodium hydroxide in 200 ml of water were dripped simultaneously onto 21.4 g of 4-chloro-1-methyl-1,5-naphthyridinium fluoro-sulfonate in 500 ml of water cooled to 10°. The reaction was stirred at ambient temperature overnight and then extracted 3 x 200 ml of chloroform. Evaporation of the dried chloroform solution yielded 7.5 g of the titled compound.

6-Butoxy-4-chloro-1-methyl-1,5-naphthyridine-2-one (662-61)

6-Butoxy-4-chloro-1,5-naphthyridine was reacted with methyl-fluorosulfonate as previously described. The naphthyridinium salt was isolated as a methylene chloride soluble material in quantitative yield, mp 92-5°.

Solutions of 6.1 g of NaOH in 50 ml of H_2O and 19.5 g of potassium ferricyanide in 75 ml of H_2O were dripped simultaneously into a chilled solution, 6.1 g of the above naphthyridinium salt in 200 ml of H_2O. An orange precipitate formed and gradually turned yellow. After 3 hours, the reaction was filtered and the filtercake water washed. Yield 3.5 g (78%), mp = 123-5° (C_7).

Anal calcd for $C_{13}H_{15}ClN_2O_2$: %C, 58.65; %H, 5.64; %N, 10.53: Found: %C, 58.46; %H, 5.52; %N, 10.32

6-Butoxy-1-methyl-1,5-naphthyridin-4-one (662-28)

A dilute caustic solution of the naphthyridinium salt when heated on a steambath for several hours and extracted with $CHCl_3$ yielded the titled compound as a white solid, mp 173-5° (Ph/C_7).

Anal calcd for $C_{13}H_{16}N_2O_2$: %C, 67.57; %H, 7.00; %N, 12.16: Found: %C, 67.24; %H, 6.90; %N, 12.07

4-Chloro-1-methyl-1,5-naphthyridin-2,6-dione (662-34)

A solution of 2 g of 6-butoxy-4-chloro-1-methyl-1,5-naphthyridin-2-one in 30 ml of concentrated HCl was heated on a steambath overnight. The solution was diluted with three volumes of H_2O, cooled, and filtered. Sublimation of ∿210° gave a 95% yield of the titled compound as a yellow solid, mp 290°.

Anal calcd for $C_9H_7ClN_2O_2$: %C, 51.43; %H, 3.33; %N, 13.33: Found: %C, 50.98; %H, 3.53; %N, 13.24

5.3 Amino Sidechains

4-Acetamido-1-Hexanol (655-97)

Acetic anhydride, 11.2 g, was added, dropwise, to 11.7 g of 4-amino-1-hexanol in 80 ml of EtOH at room temperature. After addition was complete, the reaction was refluxed for 1 hour and distilled. The titled compound was isolated as a viscous liquid, $b_{0.13\ mm}$ = 143°, in >95% yield.

4-Acetamido-1-pentanol (655-125)

Acetic anhydride was reacted with 4-amino-pentanol as described above to give the titled compound in 95% yield, $b_{0.2\ mm}$ = 143°.

4-Acetamido-1-hexylphthalimide (662-55)

Triphenylphosphine, 39 g, in 125 ml of dry THF, was gradually added to a cooled solution of 23.75 g of 4-acetamido-1-hexanol, 21.9 g, phthalimide, and 25.9 g of diethyl azodicarboxylate in 700 ml of dry THF, at 20-25°. The reaction was stirred at ambient temperature overnight and the solvent removed at reduced pressure. Addition of 300 ml of Et_2O to the residue resulted in formation of a heavy precipitate. The product was filtered and washed with Et_2O. Yield 33 g (77%), mp 151-2° (pH/C_6).

Anal calcd for $C_{16}H_{20}N_2O_3$: %C, 66.67; %H, 6.94; %N, 9.72: Found: %C, 67.19; %H, 6.89; %N, 9.99

4-Acetamido-1-pentylphthalimide (655-135)

4-Acetamido-1-pentanol was converted to the titled compound in the manner detailed above. Yield 75%, mp 160-2° (H_2O).

Anal calcd for $C_{15}H_{18}N_2O_3$: %C, 65.69; %H, 6.57; %N, 10.22: Found: %C, 65.30; %H, 6.57; %N, 10.20

4-Acetamido-1-hexylamine (662-51)

A solution of 21 g of 4-acetamido-1-hexylphthalimide, and 7 g of hydrazine in 500 ml of methanol was refluxed for 2.5 hours. The solvent was removed under vacuum and the residue dissolved in 500 ml of 20% NaOH. Extraction with 500 ml of THF, solvent evaporation and distillation yield (79%) of the titled amine as a viscous oil, $b_{0.05\ mm}$ = 138-140°.

Anal calcd for $C_8H_{18}N_2O$ %C, 60.76; %H, 11.39; %N, 17.72: Found: %C, 60.54; %H, 11.38; %N, 17.37

4-Acetamido-1-pentylamine (655-143)

The titled compound was obtained in the manner described above, $b_{0.05\ mm}$ = 113-115°.

Anal calcd for $C_7H_{16}N_2O$: %C, 58.33; %H, 11.11; %N, 19.44: Found: %C, 57.92; %H, 10.85; %N, 19.02

4-Phthalimido-1-bis-(p-chlorophenyl) sulfenimido pentane (662-40)

To a solution of 0.095 mole of lithium-bis-(p-chlorophenyl) sulfenimide in 200 ml of THF at -30° was added 0.1 mole of 4-phthalimido-1-pentyl iodide in 82 ml of THF. Reaction temperature was kept at -30 for 2 hours after addition and then at ambient temperature overnight. The solvent was removed under vacuum and the residue dissolved in ether, extracted with cold water, dried and evaporated. The viscous residue solidified when slurried with hexane. The titled compound, mp 91-2°, was isolated in 72% yield.

Anal calcd for $C_{25}H_{22}Cl_2N_2O_2S_2$: %C, 58.14; %H, 4.26; %N, 5.43: Found: %C, 58.15; %H, 4.30; %N, 5.50

5-Acetamido-2-pentyl phthalimide (655-123)

Dissolution of the sulfenimide in ether and saturation of the ether with gaseous HCl precipitated 4-acetamido-2-pentylamine hydrochloride, mp 81-6°, in >80% yield.

Without further purification, the amine hydrochloride, 10 g, was dissolved in 100 ml of warm acetic anhydride and treated, dropwise, with 15 ml of triethylamine. After ~0.5 hours the precipitate of triethylamine hydrochloride was filtered and the filtercake washed with ether. The combined liquid phase was concentrated at reduced pressure, and the viscous residue stirred with cold dilute aqueous caustic. The product precipitated as a white solid in 60% yield, mp 137-8° (PhH/hexane).

Anal calcd for $C_{15}H_{18}N_2O_3$: %C, 65.69; %H, 6.57; %N, 10.22: Found: %C, 66.05; %H, 6.56; %N, 10.50

5-Acetamido-2-pentylamine (662-58)

Reaction of the above material with hydrazine in methanol as previously described gave an 80% yield of the titled amine as a viscous oil, $b_{0.05\ mm} = 114°$.

Anal calcd for $C_7H_{16}N_2O$: %C, 58.33; %H, 11.11; %N, 19.44: Found: %C, 58.57; %H, 11.40; %N, 18.92

3-(1,3-Dioxalanyl)-1-butylcyanide (655-31)

A solution of 20 g of 3-keto-1-butylcyanide, 14 g of ethylene glycol, and 1.1 g of TsOH was heated at reflux with a Dean-Stark head until the calculated amount of water was collected. Distillation yielded the titled compound, $b_{0.2\ mm} = 78°$.

4-(,3-Dioxolanyl)-1-pentylamine (655-36)

The reduction of 655-31 by $LiAlH_4$ in Et_2O by the usual procedure yielded the titled amine, $b_{7\ mm} = 83°$.

Anal calcd for $C_7H_{15}NO_2$: %C, 57.89; %H, 10.41; %N, 9.64: Found: %C, 56.36; %H, 9.70; %N, 9.15

5.4 Miscellaneous Intermediates

4-Amino-1,5-Naphthyridin-2-one (662-22)

One gram of 4-chloro-1,5-naphthyridin-2-one in 30 ml of ethanol saturated with gaseous ammonia was heated at 170° for 18 hours in a glass pressure reactor. After evaporation of the solvent the residue was vacuum sublimed at 100°. The titled compound was isolated in 67% yield, mp 236-7°.

Anal calcd for $C_9H_9N_3O$: %C, 61.71; %H, 5.14; %N, 24.00: Found: %C, 62.03; %H, 5.29; %N, 24.39

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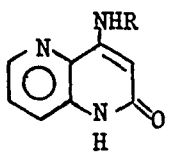
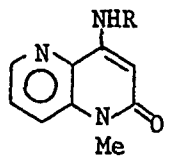
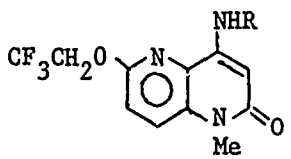
7. BIOLOGICAL ACTIVITY DATA

Test data for the target naphthyridin-2-one drugs which have to date been evaluated as antimalarial agent are summarized.

7.1 Plasmodium Cynomolgi (B Strain)

WRAIR No.	Structure*	Daily Dose Mg/Kg	Response: Relapse	Response: Days Between R_x and Relapse	Response: Infection Cured
206287		1.0	+	7	-
		10.0	-	-	+
222119		0.5	+	13	-
		1.0	-	-	+
		3.33	+	7	-
222121		0.5	+	9	-
		1.0	-	-	+
		3.33	+	9	-

*R = $-(CH_2)_5NH$-i-Pr

7.2 Plasmodium Berghei (KBG 173 Strain)

Compound: Code No.	Compound: WRAIR No.	Activity (T-C)[a]: 40 mg/Kg	160	320	640[b]
NT-27	BG89362	0.2	0.2		0.3(2)
NT-30	BH01014	0.2	0.2		0.2
NT-31	BH01032	0.2	0		0(5)
NT-32	BH12759	0.2	0.4		0.2
NT-33	BH12768	0.2	0.2		0

(a) T-C represent survival time of the test animal minus the control, in days, at the indicated dose levels.
(b) Toxic deaths are indicated in parenthesis.

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18. SUPPLEMENTARY NOTES

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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Antimalarials
Naphthyridinone
Masked 1,4-pentane diamines

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

4-Amino-1,5-naphthyridines have been envisioned as structural contours of both 4-amino and 8-aminoquinoline antimalarial agents. These derivatives have, however, only been effective against the asexual erythrocytic stages of the parasite. None of the reported variations show the prophylactic behavior characteristic of 8-aminoquinoline drugs. Recently we reported that oxidation of the 1,5-naphthyridine nucleus to the 1,5-naphthyridin-2-one resulted in drugs responsive to the Schmidt prophylactic antimalarial screen.

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20. Abstract (Cont'd)

The work detailed herein was an attempt to amplify ~~on our~~ earlier ~~finding~~ through (a) further alterations of the naphthyridin-2-one nucleus and (b) attachment of diamino sidechains noted to be significant to the prophylactic agents pamaquine, pentaquine, primaquine, and quinocide. The latter two types of sidechains received particular emphasis.

In general, target drugs were obtained in 50-90% yield by a high temperature reaction of a diaminoalkane with a 4-chloro-1,5-naphthyridin-2-one. Although 1-(H) and 1-Me naphthyridinone syntheses have been reported we experienced considerable difficulty in reproducing the reported yields and purity. Modification of the reported experimental and isolation procedure proved to be the best of several alternative synthesis of 4-chloro-1,5-naphthyridin-2-ones. A new synthetic entry into 4-chloro-1-methyl-1,5-naphthyridin-2-one synthons evolved during this contractual period. The new technique is superior to reported procedures in terms of its generality, yield, and freedom from contamination by isomeric naphthyridines. In addition, integrity of acid sensitive functionality was maintained during the synthesis of the 1-methyl 1,5-naphthyridin-2-ones. In essence the new preparative method involves N-methylation of 4-chloro-1,5-naphthyridine followed by oxidation of the naphthyridinum salt.

Seven target drugs substituted at C-4 of the 1,5-naphthyridin-2-ones by pamaquine and pentaquine sidechains were prepared. Five of these drugs was obtained by reaction of the commercially available diaminoalkane with the appropriate naphthyridinone synthon. Acid catalyzed hydrolysis of those drugs substituted by 6-butoxy functionality yielded the corresponding 6-hydroxy derivatives.

Because 1,4-pentanediamines, masked on either amino termini were unknown at the inception of this program introduction of the primaquine and quinocide sidechain into the naphthyridinone nuclei required a different synthetic approach. Attachment of the primaquine sidechain could be realized by reaction of 4-amino-1-pentanol with 4-chloro-1,5-naphthyridin-2-ones and in several steps transform the hydroxyl terminated sidechain into the primary amino function. The overall yield from this sequence of reaction is extremely poor.

Starting with 4-amino-1-pentanol a series of synthetic steps was devised which permitted us to realize synthesis of the previously unknown isomeric "masked" 1,4-pentanediamines. These isomeric aminoalkanes were readily attached to the naphthyridinone ring via the nucleophilic displacement of C-4 chlorine. The target drugs substituted by sidechains having primaquine and quinocide configuration were isolated in good yield as crystalline solids. Cleavage of the acetamido masking function from these drugs was achieved by base catalyzed hydrolysis. Acidic hydrolytic conditions destroyed the entire sidechain.

A total of 18 target drugs substituted in the 1,5-naphthyridin-2-one C-4 position by diaminoalkane functions was synthesized during this contract. No biological data is yet available.